Official Title: A Phase I, Open-Label, Single-Dose, Adaptive (S)-(-)-[18F]fluspidine and [18F]fallypride Positron Emission Tomography Study to Evaluate Sigma-1 and Dopamine-2 Receptor Occupancy by Pridopidine in the Human Brain of Healthy Volunteers and in Patients with Huntington's Disease

NCT Number: NCT03019289

Document Date: 2 May 2016

Clinical Study Protocol with Amendment 02

Study Number TV7820-IMG-10082

A Phase I, Open-Label, Single-Dose, Adaptive (S)-(-)-[^{18}F]fluspidine and [^{18}F]fallypride Positron Emission Tomography Study to Evaluate Sigma-1 and Dopamine-2 Receptor Occupancy by Pridopidine in the Human Brain of Healthy Volunteers and in Patients with Huntington's Disease

Phase 1

IND number: 77,419; NDA number: N/A; EudraCT number: 2016-001757-41

Protocol Approval Date: 02 May 2016

Protocol with Amendment 01 Approval Date: 11 November 2016

Protocol with Amendment 02 Approval Date: 06 October 2017

Sponsor

Teva Branded Pharmaceutical Products R&D, Inc.

[redacted]

Confidentiality Statement

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

AMENDMENT HISTORY

The protocol for study TV7820-IMG-10082 (original protocol dated 02 May 2016) has been amended and reissued as follows:

Amendment 02	06 October 2017 18 subjects and no patients have been enrolled to date
Amendment 01	11 November 2016 No subjects or patients have been enrolled to date

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 17.

INVESTIGATOR AGREEMENT

Original Protocol Dated 02 May 2016

Clinical Study Protocol with Amendment 02 06 October 2017

IND Number: 77,419; NDA Number: N/A; EudraCT Number: 2016-001757-41

A Phase I, Open-Label, Single-Dose, Adaptive (S)-(-)-[^{18}F]fluspidine and [^{18}F]fallypride Positron Emission Tomography Study to Evaluate Sigma-1 and Dopamine-2 Receptor Occupancy by Pridopidine in the Human Brain of Healthy Volunteers and in Patients with Huntington's Disease

Principal Investigator: Osama Sabri, MD, PhD

Title: Director and Chairman, Department of Nuclear Medicine, University of Leipzig

Address of Investigational Center: [redacted]

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

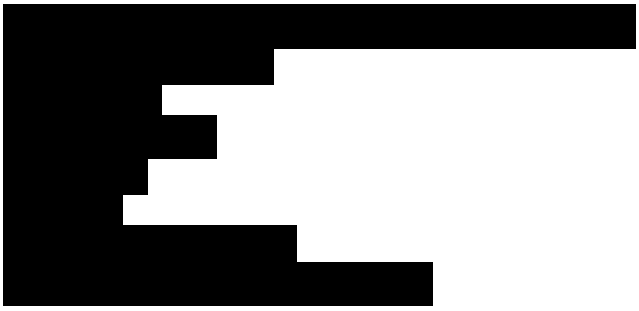
I will make available the protocol and all information on the drug that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study. I agree to keep records on all subject 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 Osama Sabri, MD, PhD	**Signature**	**Date**

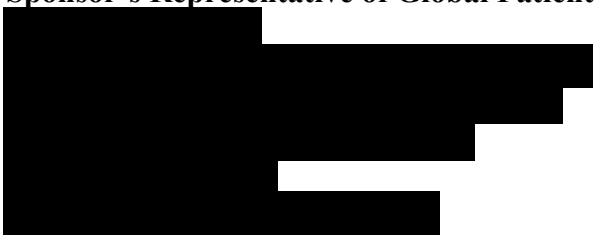
SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative [redacted]	[redacted]	**Date** 06 October 2017

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

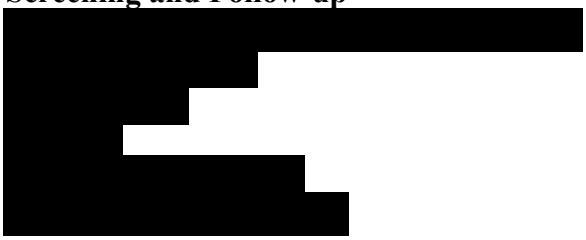


Sponsor's Representative of Global Patient Safety and Pharmacovigilance



Contract Research Organization and Image Core Laboratory

Screening and Follow-up

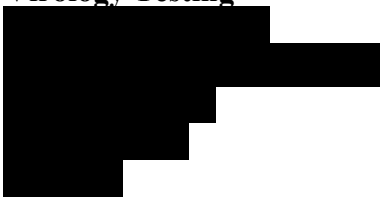


Screening MRIs

Treatment Period

Central Clinical Laboratory

Virology Testing



Bioanalysis of Pridopidine and TV-45065 in Plasma

Pharmacogenetic/Biomarker Evaluation (Sponsor)

[redacted]

Biorepository for Pharmacogenetic and Biomarker Samples

[redacted]

Pharmacogenetic Analysis

[redacted]

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

[redacted]

For operational issues, contact the operational lead listed below:

[redacted]

For protocol clinical issues, contact the study leader listed below:

[redacted]

For **serious adverse events:**

Send by email to the local safety officer (LSO) [redacted] The email address will also be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Study TV7820-IMG-10082

Title of Study: A Phase I, Open-Label, Single-Dose, Adaptive (S)-(-)-[^{18}F]fluspidine and [^{18}F]fallypride Positron Emission Tomography Study to Evaluate Sigma-1 and Dopamine-2 Receptor Occupancy by Pridopidine in the Human Brain of Healthy Volunteers and in Patients with Huntington's Disease

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

Investigational New Drug (IND) Number: 77,419 **New Drug Application (NDA) Number: N/A**
EudraCT Number: 2016-001757-41

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

Name of Investigational Product: Pridopidine (TV-7820) capsules

Phase of the Study: 1

Number of Investigational Centers Planned: 1

Countries Planned: Germany

Planned Study Period: Q1 2017 to Q1 2018

Number of Patients Planned: Up to 45 subjects are planned to be enrolled in this study to ensure up to 38 evaluable subjects (20 subjects in Part A, 15 subjects in Part B, 3 subjects in Part 0 [test-retest])

Study Population: This study will recruit healthy non-smoking men between 25 and 55 years of age (inclusive) and (optional) men aged ≥25 years with Huntington's disease (HD). Healthy subjects and HD patients who are poor cytochrome P450 (CYP) 2D6 metabolizers will be excluded from participation in this study.

Primary Objective: The primary objectives of this study are:

- To demonstrate target engagement, receptor binding/occupancy (RO) of pridopidine to sigma-1 receptors (S1R) in the brain (whole brain, cortical and subcortical regions) of healthy subjects and (optional) Huntington's disease (HD) patients after single oral dose administration;
- To establish the relationship between the plasma pridopidine concentrations and the S1R occupancy in the brain of healthy subjects and (optional) HD patients following a single oral dose of pridopidine.

Secondary Objectives: The secondary objectives of this study are:

- To establish test-retest variability of (S)-(-)-[^{18}F]fluspidine positron emission tomography (PET) imaging of S1R in healthy subjects;
- To evaluate the pharmacokinetics of pridopidine following single oral administration in healthy subjects and (optional) HD patients;
- To assess safety of pridopidine in healthy subjects and (optional) HD patients.

Exploratory Objectives: The exploratory objectives of the study are:

- [redacted]
- To explore target engagement, RO of pridopidine to the dopamine-2 receptors (D2R) in the brain of healthy subjects and (optional) HD patients;
- To explore the relationship between the plasma pridopidine concentrations and D2R occupancy in the brain of healthy subjects and (optional) HD patients following a single oral dose of pridopidine;
- To establish the relationship between the plasma metabolite TV-45065 concentrations and the S1R occupancy in the brain following a single oral dose of pridopidine to healthy subjects and (optional) HD patients;

- To evaluate the relationship between plasma pridopidine concentration and brain activity using functional magnetic resonance imaging (MRI-based Attenuation Correction [MR-AC], T1-weighted rapid 3-dimensional gradient-echo technique [T1 MPRAGE 3D]. Arterial Spin Labeling [ASL], 2D multi-voxel Magnetic Resonance Spectroscopy [MRS], and resting state functional Magnetic Resonance Imaging [rs-fMRI]);
- To evaluate the relationship between S1R and D2 receptor occupancy in vivo by pridopidine and brain activity using functional magnetic resonance imaging (MR-AC, T1 MPRAGE 3D, ASL, 2D MRS, and rs-fMRI);
- To explore any effects of pridopidine on brain activity, and link it to the occupancy of S1R and D2R;
- [redacted]

Study Endpoints:

Pharmacodynamic Endpoints

The PET acquisition, as well as advanced magnetic resonance imaging (MRI) protocols (MR-AC, T1 MPRAGE 3D, ASL, 2D MRS, and rs-fMRI) will be detailed in dedicated imaging manuals. These will also contain an analysis plan for the image data. Imaging manuals will be provided prior to initiating the study.

Pharmacokinetic Endpoints

Blood samples for analysis of pridopidine and the metabolite TV-45065 will be obtained up to 24 hours after dosing. Pharmacokinetic parameters will be calculated.

Safety and Tolerability Endpoints

The safety and tolerability endpoints are:

- occurrence of adverse events during the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results
- vital signs (blood pressure [BP], respiratory rate, body temperature, and pulse) measurements at each visit
- electrocardiogram (ECG) findings
- physical examination findings, including body weight measurements,
- use of concomitant medication during the study
- number (%) of subjects who did not complete the study (end of study)
- number (%) of subjects who did not complete the study due to adverse events

Biomarker Endpoints

Blood samples for biomarker analysis in serum, plasma, and ribonucleic acid (RNA) will be collected up to 24 hours after pridopidine dosing.

Pharmacogenetic Endpoints

A pharmacogenetic blood sample will be collected at screening for genetic analyses of the CYP2D6 metabolizer status and S1R polymorphs.

General Design and Methods: This is a Phase 1, single-dose, open-label, adaptive design (S)-(-)-[^{18}F]fluspidine PET study in healthy subjects and (optional) in patients with HD designed to demonstrate target engagement and to assess the occupancy of the S1R by pridopidine. PET with the tracer (S)-(-)-[^{18}F]fluspidine will be used to quantify

changes in S1R availability following the administration of pridopidine (Part A). Binding of pridopidine to D2R may be assessed using PET imaging with [^{18}F]fallypride (Part B, optional).

The test-retest variability of (S)-(-)-[^{18}F]fluspidine PET will be determined in up to 6 healthy subjects in parallel (Part 0).

In addition, plasma corticoid levels will be assessed immediately before each (S)-(-)-[^{18}F]fluspidine or [^{18}F]fallypride injection in all subjects.

Pharmacogenetic samples will be collected at screening for CYP2D6 and exploratory genotyping. Biomarker pharmacodynamic samples will be collected at visit 3, prior to dosing and 4, 8, and 24 hours post pridopidine dose.

Up to 45 subjects are planned to be enrolled in this study to ensure up to 38 evaluable subjects. The study will consist of a screening period of up to 8 weeks prior to first dosing, including a T1 MPRAGE 3D MRI scan (visit 1), a study period of up to 4 weeks (including visits 2 and 3), and a follow-up visit (visit 4). During the study period, the subjects will undergo a baseline PET investigation (PET session 1) at visit 2, and subsequently a post-treatment PET investigation (PET session 2) following a single oral dose of pridopidine at visit 3. Each dose cohort will comprise up to 4 subjects. It is expected that each dose cohort within Part A or Part B will receive a different dose of pridopidine; however, subjects within each cohort will be administered the same dose (deviation will also be allowed). It is possible that subjects in different cohorts within Part A or Part B may receive the same dose of pridopidine if timing of the PET imaging is changed or unchanged (eg, cohort with HD patients).

Subjects in Part A and B may receive the same dose of pridopidine for different tracers or different populations (healthy volunteers or patients with HD). The maximal dose of pridopidine administered will not exceed 90 mg in healthy subjects or 112.5 mg in HD patients (the highest dose investigated in the PRIDE-HD study).

Up to 20 subjects may be evaluated in Part A, although it is expected that study objectives may be achieved with fewer subjects (more subjects will also be allowed). At the day of each PET session, prior to PET imaging, a cubital or forearm vein will be cannulated to inject (S)-(-)-[^{18}F]fluspidine and (at visit 3 only) to obtain venous blood samples for quantification of pridopidine and its metabolite TV-45065, and also for other exploratory biomarker analysis. The subject's radial artery on the other arm (or the same arm if this cannot be achieved) will be cannulated to obtain arterial blood samples during PET imaging for the quantification of plasma radioactivity associated with (S)-(-)-[^{18}F]fluspidine, in order to estimate a metabolite-corrected arterial plasma input function for PET data analysis.

The PET imaging will consist of subsets of PET scans that will be acquired in list mode: 4 blocks with breaks in between. The first PET acquisition block of 90 minutes duration (0 to 90 minutes) will be started together with the intravenous injection of 300±30 MBq (S)-(-)-[^{18}F]fluspidine; the following acquisition blocks of 30 minutes duration each will be started at 2, 3, and 6 hours post-injection of the PET tracer. Each PET acquisition block will be acquired in list mode in order to allow variable subdivision into multiple time frames as detailed in the imaging manual. In an effort to facilitate easier PET procedure for HD patients after the first 90-minute PET acquisition block, the subsequent 30-minute PET acquisition blocks are made optional per Investigator's judgement.

The first dose of pridopidine will be high (90 mg) for subjects enrolled in the first dose cohort but may be changed to another dose based on PRIDE-HD study results. Subsequent doses (0.5 or 1 mg in healthy subjects; 2.5, 5, 10, 22.5, 45, or 67.5 mg in healthy subjects and HD patients; and a high dose of 112.5 mg in HD patients) will be determined on the basis of the RO results following PET session 2 and the time-activity profiles of (S)-(-)-[^{18}F]fluspidine from previous cohort subjects. In addition, the timing of the PET sessions may also be revised. If any of the postdose PET investigations are compromised due to technical or logistic reasons, a repeat investigation may be considered, provided that the resulting cumulative radiation exposure by (S)-(-)-[^{18}F]fluspidine for all PET sessions does not exceed the allowed overall study exposure (effective dose not exceeding 20 mSv), when using

tracer administered activity of 300±30 MBq per PET session, and further respecting a washout of 7 days of pridopidine and its metabolites. PET session 2 will start at 2 hours postdose of pridopidine.

Up to 15 subjects may be evaluated in Part B to characterize the D2R binding of pridopidine. The cohort structure will also comprise up to 4 subjects. Each of the 2 PET sessions will consist of 4 subsets of acquisition blocks that will be acquired in list mode: 0 to 90 minutes, 120 to 150 minutes, 180 to 210 minutes, and 360 to 390 minutes post-injection of 200±20 MBq [^{18}F]fallypride. Each PET acquisition block will be acquired in list mode in order to allow variable subdivision into multiple time frames, and will be according to the institutional standard as detailed further in the imaging manual. PET session 2 will start at approximately 2 hours postdose of pridopidine. The PET imaging protocol is essentially the same as for (S)-(-)-[^{18}F]fluspidine. From the second block onwards, acquisition can commence within ±10 minutes of the nominal time, but the duration should still be 30 minutes for each of these blocks. In an effort to facilitate easier PET procedure for HD patients after the first 90-minute PET acquisition block, the subsequent 30-minute PET acquisition blocks are made optional per Investigator's judgement.

Brain MRI scans will be performed at screening to ensure subjects are qualified for the study but will also provide data to aid the analysis of PET data. Additional functional MRI scans (MR-AC, T1 MPRAGE 3D, ASL, 2D MRS, and rs-fMRI) will be performed in parallel with the PET imaging sessions to evaluate the relationship between brain activity and S1R or D2 receptor occupancy by pridopidine.

The dose of pridopidine in Part B will be determined based on the results obtained using (S)-(-)-[^{18}F]fluspidine in Part A. The timing of the [^{18}F]fallypride PET scan may also be revised. If any of the postdose PET investigations are compromised due to technical or logistic reasons, a repeat investigation may be considered, provided that the resulting cumulative [^{18}F]fallypride dose for all PET sessions does not exceed the authorized overall study exposure (effective dose not exceeding 20 mSv), when using tracer administered activity of 200±20 MBq per PET session, and further respecting a washout of 7 days of pridopidine and its metabolites.

Blood samples for determination of pridopidine and TV-45065 plasma concentrations and exploratory biomarkers will be collected during the timing of the PET examinations in visit 3.

Safety and tolerability (the number [%]) of healthy subjects and HD patients who failed to complete the study due to adverse events) will be assessed throughout the study by monitoring adverse events and by conducting clinical safety laboratory tests, ECG, physical examination, and vital sign assessments.

Method of Randomization and Blinding: This is a non-randomized, open-label study and there is no blinding.

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

Investigational Product:

In this study, pridopidine can be administered as 0.5 or 1 mg in healthy subjects (Part A only); 2.5, 5, 10, 22.5, 45, 67.5, or 90 mg in healthy subjects and HD patients; and a higher dose of 112.5 mg may also be administered to HD patients. The applicable dose will be given selecting the lowest possible number of capsules. Pridopidine will be administered orally with 240 mL of water.

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

If lower pridopidine doses will be required, it will be prepared on site as follows:

- 0.5 and 1 mg – size 2 capsules will be filled with the appropriate amount of blend taken from the drug product capsules and diluted with [redacted]

- 2.5 mg pridopidine – size 2 capsules will be filled with the appropriate amount of blend taken from the drug product capsules
- 5 and 10 mg pridopidine – size 2 capsules will be filled with the appropriate amount of the active ingredient (neat)

Tracers:

The radiolabeled PET tracer [^{18}F]fluspidine for the neuroimaging of S1R receptors with PET will be administered as a single intravenous bolus for each PET scan, not exceeding 330 MBq and <50 μg mass.

The radiolabeled PET tracer [^{18}F]fallypride will be administered as a single intravenous bolus for each PET scan, not exceeding 220 MBq and <2 μg mass.

Duration of Patient Participation: Total study duration for each subject is expected to not exceed 12 weeks, with recruitment and screening lasting up to 8 weeks and the study period for each subject lasting up to 4 weeks.

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

a. Male subjects between 25 and 55 years (inclusive) of age, with a body mass index (BMI) ≥18.0 to ≤30 kg/m^2 and a body weight of at least 50 kg (inclusive).
b. In general, good physical and mental health as determined by medical history and psychiatric history, suicidality assessment, physical examination, 12-lead ECG, vital signs, and clinical laboratory tests. A subject with a clinical abnormality in the laboratory profile or BP can be included only if the investigator or his designee considers that the abnormality does not introduce an additional risk factor for the subject's health, or interfere with the study objectives.
c. Men who are potentially fertile (not surgically [eg, vasectomy] or congenitally sterile), whose female partners are of childbearing potential, must use contraception for the duration of the study and for 90 days after discontinuation of study drug (because of the possible effects on spermatogenesis). Highly effective methods of contraception are those with a failure rate of less than 1% per year (eg, female partner's use of hormonal contraceptive [oral, implanted, transdermal, injected], female partner's use of an intrauterine device [IUD]), and barrier method with spermicide. In addition, male subjects may not donate sperm for the duration of the study and for 90 days after discontinuation of study drug.
d. Are able to understand the requirements of the study; are willing to comply with the requirements of the study (eg, imaging procedures, all dietary, exercise, and alcohol restrictions) and provided their written informed consent to participate in the study.
e. Willing to provide a blood sample for genetic analyses (including CYP2D6 status, S1R polymorphs, genetic long QT syndrome in subjects who had QT prolongation following study drug administration or any other genetic analyses related to pridopidine response) at the screening visit.

Patients with Huntington's disease:

a. Diagnosis of HD based on clinical features and the presence of ≥36 cytosine-adenosine-guanine (CAG) repeats in the huntingtin gene.
b. Male age ≥25 years, with an onset of HD after 18 years of age.
c. Men who are potentially fertile (not surgically [eg, vasectomy] or congenitally sterile), whose female partners are of childbearing potential, must use contraception for the duration of the study and for 90 days after discontinuation of study drug (because of the possible effects on spermatogenesis). Highly effective methods of contraception are those with a failure rate of less than 1% per year (eg, female partner's use of hormonal contraceptive [oral, implanted, transdermal, injected], female

partner's use of an IUD), and barrier method with spermicide. In addition, male patients may not donate sperm for the duration of the study and for 90 days after discontinuation of study drug.

d. Body weight ≥50 kg.
e. A sum of ≥25 points on the UHDRS-TMS at the screening visit.
f. 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.
g. Willing to provide a blood sample for genetic analyses (including CAG analysis, CYP2D6 status, S1R polymorphs, 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.
h. Willing and able to take oral medication and able to comply with the study specific procedures.
i. Ambulatory, being able to travel to the study center, and judged by the investigator as likely to be able to continue to travel for the duration of the study.
j. Availability and willingness of a caregiver, informant or family member to accompany the patient to the clinic at study visits. The suitability of the caregiver should be judged by the investigator.
k. 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 (visit 2, day -1) and must be kept constant during the study.
l. Are able to understand the requirements of the study; are willing to comply with the requirements of the study (eg, imaging procedures, all restrictions) and provided their written informed consent to participate in the study.

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

Healthy Subjects:

a. CYP2D6 poor metabolizers
b. The subject has been previously exposed to ionizing radiation or radioactive substances as a result of clinical research or medical treatment in the past 10 years.
c. The subject has large scale tattoos, in particular involving the head and neck area.
d. The subject has a counterindication to having an MRI, including (but not limited to):
   - The presence of metal implants (excluding metal dental crowns) that could affect MRI imaging OR
   - has worked with ferrous metals either as a vocation or hobby (for example sheet metal worker, welder or machinist) in such a way that might have led to unknown indwelling of metal fragments that could cause injury if moved in response to the magnetic fields during the MRI imaging.
e. The subject suffers from claustrophobia or needle phobia.
f. The subject has a finding on screening MRI that will, in the opinion of the principal investigator (PI) impair the safety of the subject or the scientific integrity of the study.
g. The subject has a known coagulation abnormality.
h. Parts A and 0 only: Individuals who had evidence of only one patent arterial supply to the hand (modified Allen test).
i. Any current or history of heart condition or increased pro-arrhythmic risk, including:
   - History of cardiovascular disease (eg, coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension, deep vein thrombosis, pulmonary embolism, family history of thrombophilia)
   - History of Long QT Syndrome or a first degree relative with this condition

- Family history of sudden death/Brugada syndrome
- A prolonged Fridericia-corrected QT (QTcF) interval (defined as a QTcF interval of >450 msec) at the screening or admission (baseline) visit(s). If there is evidence of a prolonged QTcF interval from the initial (single) measurement, then the ECG can be repeated twice, and the mean of the 3 screening measurements will be used to determine whether or not the subject is suitable for inclusion in the study.
- Any repolarization deficits
- Untreated hypokalemia and/or untreated hypomagnesaemia
- Unclear syncopes
- Any other clinically significant abnormal ECG as judged by the investigator.

j. Creatinine clearance <90 mL/min at screening, calculated using the Cockcroft-Gault equation. It is permitted to repeat the test once, if clinically appropriate.

k. Hemoglobin value below the lower limit of the reference range and evaluated by the investigator to be clinically significant.

l. Positive serology for human immunodeficiency virus (HIV-1, HIV-2), hepatitis B surface antigen (HBsAg), and/or hepatitis C.

m. Presents or has a history of clinically significant diseases of the renal, hepatic, gastrointestinal, cardiovascular, musculoskeletal, immunological, endocrine (including diabetes even if controlled by diet), metabolic diseases, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs, as judged by the investigator.

n. History of alcohol, narcotic, or any other substance dependence in the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013).

o. History of clinically significant psychiatric diseases, such as major depressive disorder or anxiety, as judged by the investigator.

p. Subjects with adverse events of suicidal ideation or attempt at any time in the past or as measured by suicide ideation score of ≥3 on the Columbia-Suicide Severity Rating Scale (C-SSRS, screening version), or subjects who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) if the attempt or acts were performed at any time in the past, or subjects who, in the opinion of the investigator, present a risk of suicide.

q. Has had one of the following conditions:
- major trauma or surgery in the 2 months before screening or at any time between screening and admission
- acute/chronic infection within 2 weeks before screening or at any time between screening and admission
- malignancy within the last 5 years
- epilepsy, seizure, convulsions or syncope (including febrile seizures)
- history of tuberculosis
- BP outside the range of 90 to 139 mmHg (systolic) or 55 to 89 mmHg (diastolic); or pulse rate outside the range of 45 to 99 bpm; all measured after 5 minutes rest in seated or supine position. Vital signs may be retested twice at intervals of 5 minutes.

r. Not willing or able to refrain from intensive physical exercise during the study.

s. Current or history of clinically significant allergy or known hypersensitivity to any ingredients of the study medication [redacted]

t. Planned medical treatments (excluding dental care) during the study period, which may interfere with the study.
u. Use of one of the following prohibited drugs, substances, or foods as follows:
   - an investigational drug (new chemical entity) within 6 weeks prior to the first day of study drug administration or within 5 half-lives (whichever is longer)
   - any monoamine oxidase inhibitors within 14 days before the first day of study drug administration
   - any other medications (including over-the-counter medications, vitamins, or herbal or nutritional supplements) within 7 days before the first day of study drug administration (except paracetamol/acetaminophen or ibuprofen used occasionally, up to 24 hours before the first day of study drug administration)
   - drugs known to significantly inhibit CYP2D6 enzyme drug metabolism within 21 days prior to the first day of study drug administration or within 5 half-lives (whichever is longer) before the first day of study drug administration, or drugs known to significantly induce CYP enzyme drug metabolism within 28 days before the first day of study drug administration
   - drugs known to cause significant QT-prolongation such as anti-arrhythmic drugs or antidepressants within 28 days before the first day of study drug administration
   - daily consumption of more than 6 units of caffeine and/or xanthine-containing products, within 2 weeks before the first dose of study drug, or not able to refrain from consumption of more than 2 units of caffeine-containing foods or drinks from 48 hours prior to admission visit and discharge. One caffeine unit is contained in the following items: 1 cup of coffee, 2 cans of cola, 1 cup of tea, ½ cup of energy drink (eg, Red Bull) or 3 chocolate bars. Subject should be able to abstain from caffeine intake for 20 hours during any day.
   - cigarette smoking (defined as >5 cigarettes per week) or use of other nicotine-containing products (eg, snuff, nicotine patch, nicotine chewing gum, mock cigarettes, or inhalers). Ex-smokers should have ceased smoking at least 6 months before screening.
   - any food or drink/beverage containing alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, brussel sprouts, mustard), and charbroiled meats within 7 days before the first day of study drug administration until after the last day of pharmacokinetic sampling.
   - a positive urine drug test or a positive alcohol breath analyzer test at admission visits, or not willing or able to refrain from illicit drugs during the study.
v. Donation or reception of any blood products (eg, plasma, platelets, etc) in the 1 month before the first day of study drug administration, or has made more than 2 donations within the 12 months preceding the first day of study drug administration, or plans to donate during the study or during the 1 months after the last study visit.
w. The subjects cannot participate or successfully complete the study, in the opinion of the investigator, for any of the following reasons:
   - The subject is mentally or legally incapacitated, or unable to give consent for any reason.
   - The subject is in custody due to an administrative or a legal decision, or under tutelage, or being admitted to a sanitarium or social institution.
   - The subject is unable to be contacted in case of emergency.
   - The subject is an employee of the site or a relative of an employee at the site.
   - Any other reason, at the discretion of the investigator.

<u>Patients with Huntington's disease:</u>

a. CYP2D6 poor metabolizers

b. The patient has been previously exposed to ionizing radiation or radioactive substances as a result of clinical research or medical treatment in the past 10 years.
c. The patient has large scale tattoos, in particular involving the head and neck area.
d. The patient has a counterindication to having an MRI, including (but not limited to):
   – The presence of metal implants (excluding metal dental crowns) that could affect MRI imaging OR
   – has worked with ferrous metals either as a vocation or hobby (for example sheet metal worker, welder or machinist) in such a way that might have led to unknown indwelling of metal fragments that could cause injury if moved in response to the magnetic fields during the MRI imaging.
e. The patient suffers from claustrophobia or needle phobia.
f. The patient has a finding on screening MRI that will, in the opinion of the PI impair the safety of the subject or the scientific integrity of the study.
g. The patient has a severe motor impairment that might cause artifacts.
h. The patient has a known coagulation abnormality.
i. Parts A and 0 only: Individuals who had evidence of only one patent arterial supply to the hand (modified Allen test).
j. 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.
k. 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 first admission, 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, (iv) history of deep vein thrombosis or pulmonary embolism, and/or (v) family history of thrombophilia.
l. Patients with a known history of Long QT Syndrome or a first degree relative with this condition.
m. Patients with a history of epilepsy or of seizures within the last 5 years.
n. 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, endocrine [including controlled diabetes], gastrointestinal, and metabolic diseases) 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.
o. 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.
p. Patients receiving medications (within the last 6 weeks prior to baseline [visit 2, day -1]) 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.

q. Patients receiving medications (within the last 6 weeks prior to baseline [visit 2, day -1]) that are metabolized by CYP2D6 and have the potential of reducing seizure threshold.
r. Creatinine clearance <60 mL/min at screening, calculated using the Cockcroft-Gault equation: (140 - age) × mass (kg) / 72 × serum creatinine (mg/dL).It is allowed to repeat the test once, if clinically appropriate.
s. 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 enters the study.
t. Alcohol and/or drug abuse within the 6 months prior to screening, as defined by the DSM-5 (American Psychiatric Association 2013).
u. Patients with adverse events of suicidal ideation or attempt at any time in the past or as measured by suicide ideation score of ≥3 on the C-SSRS (screening version), or patients who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) if the attempt or acts were performed at any time in the past, or patients who, in the opinion of the investigator, present a risk of suicide.
v. Patients with known intracranial neoplasms, vascular malformations, history of cerebrovascular accident, or intracranial hemorrhage.
w. Current or history of clinically significant allergy or known hypersensitivity to any ingredients of the study medication [redacted]
x. Treatment with tetrabenazine within 6 weeks of study baseline (visit 2, day -1).
y. Treatment with any investigational product within 6 weeks prior to the first day of study drug administration or within 5 half-lives (whichever is longer) or patients planning to participate in another clinical study assessing any investigational product during the study.
z. Use of one of the following prohibited substances, or foods as follows:
   – any food or drink/beverage containing alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, brussel sprouts, mustard), and charbroiled meats within 7 days before the first day of study drug administration until after the last day of pharmacokinetic sampling.
   – a positive urine drug test or positive alcohol breath analyzer test at admission visits, or not willing or able to refrain from illicit drugs during the study.
aa. Positive serology for HIV-1, HIV 2, HBsAg, and/or hepatitis C.

Measures and Time Points:

Pharmacodynamic Measure and Time Point:

- PET acquisition up to 390 minutes after injection of the tracer.

Safety Measures and Time Points:

- inquiries about adverse events at every visit
- clinical laboratory (serum chemistry, hematology, and urinalysis) tests on day -1 at visits 2 and 3 and at the follow up (visit 4)
- vital signs (BP, respiratory rate, body temperature, and pulse) measured at every visit
- an ECG recorded at every visit
- physical examinations on day -1 at visits 2 and 3 and at the follow up (visit 4)
- inquiries about use of concomitant medication at every visit

Pharmacokinetic Measures and Time Points:

- Collection of blood samples up to 24 hours postdose for calculation of pharmacokinetic parameters for pridopidine and its metabolite TV-45065 in plasma

Exploratory Measures and Time Points:

- Endogenous corticoid plasma levels, taken directly prior to tracer dosing
- MR-AC, T1 MPRAGE 3D, ASL, MRS, and rs-fMRI scans in parallel with the PET imaging
- Blood exploratory biomarkers including prolactin, BDNF, monoamines and histamine metabolites up to 24 hours after dosing
- A pharmacogenetic blood sample will be collected at screening for genetic analyses of the CYP2D6 metabolizer status and S1R polymorphs

Allowed and Prohibited Medications before and during the Study: For healthy subjects, other than study drug, no drug is allowed during the study, except for the occasional use of paracetamol/acetaminophen or ibuprofen. Prohibited medication restrictions will be applied to any HD patients that participate in the study.

Statistical Considerations:

Sample Size Rationale: This PET study is exploratory in nature; therefore, no formal hypothesis testing is planned. Thus, based on clinical and practical considerations, a sample size of up to approximately 38 subjects (up to 4 subjects per dose level) is considered adequate for this type of study and to attain the study objectives. Up to 45 subjects are planned to be enrolled in this study to ensure up to 38 evaluable subjects. Adaptive study design will allow increasing or reducing the study total sample size or each dose/time cohort as necessary. This sample size may include up to 4 patients with HD, which may be added to study engagement of pridopidine to the D2R and to explore the effects of neurodegeneration. It is anticipated that 3 dose levels will be sufficient to characterize the exposure-response profile. However, additional cohorts may be studied.

Pharmacodynamic Analysis:

Appropriate analysis will be performed to estimate the S1R binding potential and RO. Available evidence suggests that there is no viable reference region in the brain for (S)-(-)-[^{18}F]fluspidine that can be used for modeling purpose. Therefore, metabolite-corrected arterial plasma input function will be estimated and used in the calculation of regional PET volume of distribution (V_T), regional binding potential (BP_{ND}) and RO defined as the treatment-induced relative change in the concentration in the available receptor density as:

$$RO = \left(1 - \frac{BP_{ND}(treatment)}{BP_{ND}(baseline)}\right) \times 100\%$$

Where BP_{ND}(treatment) is the binding potential under the treatment condition and BP_{ND}(baseline) the binding potential at baseline. The BP_{ND} is a parameter proportional to the density of the available receptors and the affinity of the tracer to the receptor.

Due to the fact that a reference region most likely does not exist the following procedure is likely be used to derive the relevant PET parameters:

- V_T, representing the total radioligand in tissue (ie, free, non-displaceable and specifically bound) and a global non-displaceable volume of distribution (V_{ND}) will be calculated for each brain region and for each postdose scan using appropriate compartmental models.
- V_T and V_{ND} will allow the estimation of BP_{ND}, and the global occupancy.

RO expressed as a percentage will be calculated for each subject and each postdose scan. Spatial normalization of the PET scan to a brain atlas template will be performed using a corresponding MRI scan. All PET parameters will be calculated globally, for the whole brain, and for specific predefined brain areas.

The occupancy data for the study will be combined with the plasma concentration of pridopidine and used to derive the in vivo affinity of pridopidine for the S1R and the time-course of the occupancy of S1R by pridopidine.

Test-retest variability of (S)-(-)-[^{18}F]fluspidine uptake will be estimated using 2 baseline (S)-(-)-[^{18}F]fluspidine scans in up to 6 subjects. This will be used to calculate the uncertainty of the RO estimate.

The analysis using [^{18}F]fallypride will be similar to that using (S)-(-)-[^{18}F]fluspidine.

For calculation of BP_{ND} and RO for [^{18}F]fallypride a tissue reference model can be used using the cerebellum as reference region without specific binding.

Pharmacokinetic Analysis: Pharmacokinetic parameters will be calculated for pridopidine and its metabolite TV-45065 in the plasma using non compartmental methods, when possible. No formal statistical analyses of the pharmacokinetic data will be performed. All data will be listed and summarized descriptively by cohort (dose) and status (healthy subject or HD patient) and presented in tabular and graphical form where appropriate.

Pharmacokinetic/Pharmacodynamic Analysis:

The relationship between the pridopidine plasma concentrations and the RO will be explored graphically. If possible, an exposure-response model will be developed to quantitatively define the relationship between RO and pridopidine exposure. It will be based on the following E_{max} model (equation) to fit the pharmacokinetic-pharmacodynamic (PK/PD) data.

$$E = \frac{E_{\max} \times C}{EC_{50} + C}$$

Where E represents the receptor occupancy (%); C is the plasma concentration (ng/mL) corresponding to the receptor occupancy E; E_{max} is an asymptote representing the maximum receptor occupancy (%); EC_{50} is the plasma concentration (ng/mL) corresponding to 50% of E_{max}.

Two additional parameters derived to characterize various levels of receptor occupancy are:

- EC_{80} - the plasma concentration (ng/mL) corresponding to 80% of E_{max}. It is calculated directly from the equation by substituting E=80% of E_{max} and then solving for C.
- EC_{opt} - plasma concentration (ng/mL) corresponding to optimal receptor occupancy. EC_{opt} was defined as the lowest observed plasma concentration that achieved the model estimated E_{max}.

Safety Analyses:

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

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with predefined criteria to identify potentially clinically significant values or changes, 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 subject is treated with study drug.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, subject counts and percentages will be provided. Descriptive summaries of serious adverse events, subject withdrawals due to

adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well.

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

Tolerability Variables and Analysis:

Subject tolerability assessments (the number [%] of subjects who fail to complete the study, number [%] of subjects who fail to complete the study due to adverse events, and the number of subjects who experience treatment-emergent adverse events) will be summarized.

Pharmacogenetic and Biomarker Analysis:

Levels in exploratory biomarkers will be compared to baseline and summary tables may be generated. Exploratory biomarker results will be generated at a future point and handled in a separate addendum report.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table of Abbreviations

Abbreviation	Term
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASL	arterial spin labeling
AST	aspartate aminotransferase
AUC	area under the drug concentration by time curve
$AUC_{0–24}$	area under the concentration × time curve from time 0 to 24 hours
$AUC_{0–\infty}$	area under the concentration × time curve from time 0 to infinity
$AUC_{0–t}$	area under the concentration × time curve from time 0 to time of last measurable concentration
BCRP	breast cancer resistance protein
BDNF	brain-derived neurotrophic factor
bid	twice daily
BMI	body mass index
BP	blood pressure
BP_{ND}	regional binding potential
BUN	blood urea nitrogen
CAG	cytosine-adenosine-guanine
$C_{average}$	average plasma concentration
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
C_{max}	maximum observed concentration
CNS	central nervous system
CPK	creatine phosphokinase
CPP	clinical project physician
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
D2R	dopamine-2 receptor
DHEA	dehydroepiandrosterone
DNA	deoxyribonucleic acid

Abbreviation	Term
DSM–5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	Data and Safety Monitoring Board
EC_{50}	plasma concentration corresponding to 50% of E_{max}
EC_{80}	plasma concentration corresponding to 80% of E_{max}
ECG	electrocardiography, electrocardiogram
EC_{opt}	plasma concentration corresponding to optimal receptor occupancy
EDTA	ethylenediaminetetraacetic acid
EM	extensive metabolizer
E_{max}	an asymptote representing the maximum receptor occupancy
ET	early termination
EU	European Union
FDA	Food and Drug Administration (US)
FU	Follow up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GMP	good manufacturing practice
HART	Huntington's disease ACR16 Randomized Trial
HBsAg	hepatitis B surface antigen
HD	Huntington's disease
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medical product
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LLOQ	lower limits of quantification
LSO	local safety officer
MAD	multiple ascending dose

Abbreviation	Term
MATE1	multidrug and toxin extrusion protein 1
MATE2K	multidrug and toxin extrusion protein 2-K
MedDRA	Medical Dictionary for Regulatory Activities
MermaiHD	Multinational European Multicentre ACR16 study in Huntington's Disease
mMS	Modified Motor Score
MR-AC	MRI-based Attenuation Correction
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MTD	maximum tolerated dose
n	number
NDA	New Drug Application
NOAEL	no observed adverse effect level
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OCT1	organic cation transporter 1
OCT2	organic cation transporter 2
OTC	over-the-counter
PET	positron emission tomography
P-gp	P-glycoprotein
PI	principal investigator
pi	post-injection of tracer
PM	poor metabolizer
qd	once daily
QTcF	Fridericia-corrected QT interval
RBC	red blood cell
RNA	ribonucleic acid
RO	receptor binding/occupancy
rs-fMRI	resting state functional magnetic resonance imaging
RSI	reference safety information
S1R	sigma-1 receptor
SD	standard deviation
SOC	system organ class

Abbreviation	Term
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
T1 MPRAGE	T1-weighted rapid 3-dimensional gradient-echo technique
t_{max}	time to reach maximum (peak) concentration
TMS	Total Motor Score
TV-45065	main metabolite of pridopidine
UHDRS	Unified Huntington's Disease Rating Scale
ULN	upper limit of normal
US(A)	United States (of America)
V	visit
V_d/F	apparent volume of distribution of the drug following extravascular administration
V_{ND}	global non-displaceable volume of distribution
V_T	PET total volume of distribution
WBC	white blood cell
WHO	World Health Organization
WHO Drug	World Health Organization (WHO) drug dictionary

1. BACKGROUND INFORMATION

1.1. Introduction

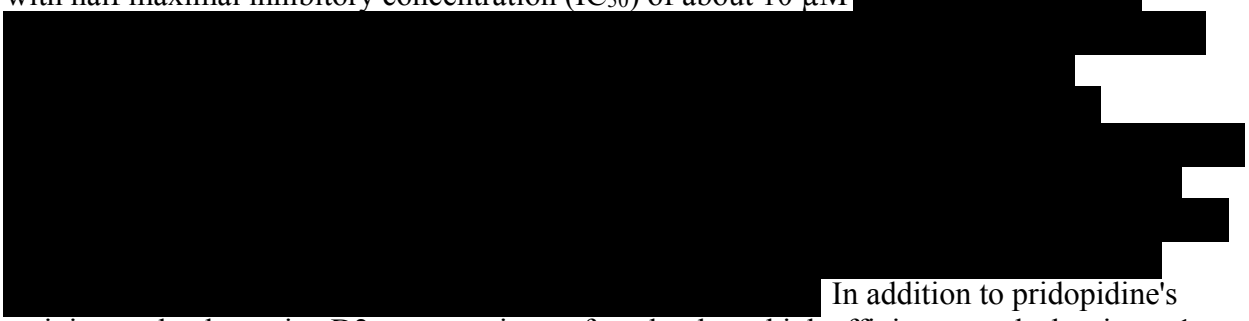
1.1.1. Huntington's Disease

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).

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

In vitro binding studies show low affinity of pridopidine for the dopamine D2 receptor (D2R) with half maximal inhibitory concentration (IC_{50}) of about 10 µM



In addition to pridopidine's activity on the dopamine D2 receptor, it was found to have high affinity towards the sigma-1 receptor (S1R) (Sahlholm et al 2013), with IC_{50} of about 100 nM (100 fold higher compared to the D2R). The S1R is a transmembrane protein located endoplasmic reticulum/mitochondria

associated membrane (Ishikawa and Hashimoto 2010) and has been implicated as potential treatment in neurodegenerative and neuropsychiatric diseases (Hayashi and Su 2004; Luedtke et al 2012). The contribution of the S1R to the mechanism of action of pridopidine and the effect on HD progression is currently under evaluation. Further information on the mechanism of action of pridopidine is provided in the current Investigator's Brochure (IB).

The expression levels and distribution of S1R is altered in neurodegenerative diseases (Mishina et al 2008; Ruscher and Wieloch 2014). Quantifying the receptor binding/occupancy (RO) by pridopidine will provide information regarding the potential to use pridopidine in the treatment of neurodegenerative diseases.

The binding of [^{18}F]fluspidine to the S1R has been demonstrated in vitro and in pigs and human study is ongoing at [redacted].
(S)-(-)-[^{18}F]fluspidine demonstrates a more favorable metabolic profile compared to its R-enantiomer, and its binding to the S1R is reversible, whereas binding of the R-enantiomer is irreversible (Fischer et al 2011).

Binding of pridopidine to the D2 receptor may also be explored using [^{18}F]fallypride. Pridopidine binds to the D2 receptor with affinity of 10 µM. Recent data suggest a role of this receptor in neurodegenerative diseases (Robertson et al 2015).

1.2. Name and Description of Investigational Product

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

Pridopidine will be provided as hard gelatin capsules. A more detailed description of the product is given in Section 3.9.

1.3. Findings from Nonclinical and Clinical Studies

1.3.1. Nonclinical Studies

Brief summaries of clinical studies are provided in the following sections. More detailed information, as well as nonclinical pharmacology, pharmacokinetics, and toxicology summaries, are provided in the current IB.

1.3.2. Clinical Studies

[redacted]

(TV7820-CNS-20002, PRIDE-HD; completed as of July 2016).. The study TV7820-CNS-20016 (Open PRIDE-HD) is a multi-center, open-label extension of the PRIDE-HD study, evaluating the safety, tolerability and efficacy of pridopidine in patients with HD. As of 11 February 2016, 89 patients were randomized in this study.

[redacted]

1.3.2.1. Clinical Pharmacology Studies

[redacted]

[redacted]

Further details may be found in the current IB.

1.3.2.1.1. Pridopidine Maximal Tolerated Dose

[redacted]

1.3.2.2. Clinical Safety and Efficacy Studies

Three randomized, double-blind, placebo-controlled, parallel-group clinical studies investigating the efficacy and safety of pridopidine in patients with HD have been conducted.
Study ACR16C007 explored the efficacy of 44 mg pridopidine once daily (qd) in 58 patients. Subsequently, the "Huntington's disease ACR16 Randomized Trial" (HART) study (ACR16C009) was designed to explore the dose-response of pridopidine looking at 3 different daily doses (10, 22.5, and 45 mg bid) in 227 patients during 12 weeks of treatment. In parallel, the "Multinational European Multicentre ACR16 study in Huntington's Disease" (MermaiHD) study (ACR16C008) investigated the efficacy and safety of 45 mg given qd and bid over 26 weeks of treatment in 437 patients.

[redacted]

Further details may be found in the current IB.

1.4. Known and Potential Benefits and Risks to Subjects

1.4.1. Known and Potential Benefits and Risks of Pridopidine

1.4.1.1. Benefits of Pridopidine

This study involves healthy subjects (with optional HD patients), and so pridopidine is not expected to provide any benefits to participants in the study.

1.4.1.2. Risks of Pridopidine

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

- [redacted]

[redacted]

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

1.4.1.2.1. 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. [redacted]

1.4.1.2.2. Pregnancy

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

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

1.4.1.2.3. Suicidal Ideation and Suicidal Attempts

[redacted]

1.4.2. Known and Potential Benefits and Risks of [^{18}F]fluspidine

1.4.2.1. Benefits of [^{18}F]fluspidine

[^{18}F]fluspidine has demonstrated potential for the neuroimaging of S1R with positron emission tomography (PET). Data from preclinical studies and preliminary data from an ongoing initial clinical trial in healthy subjects (Sigma-PET; see [redacted]) have demonstrated that [^{18}F]fluspidine binds to the S1R in the brain with a high specific uptake (Fischer et al 2011; Maisonial et al 2012), making it a suitable PET tracer for use in this study.

There are no direct benefits to the study subject from exposure to [^{18}F]fluspidine in this trial.

1.4.2.2. Risks of [^{18}F]fluspidine

The mass dose of [^{18}F]fluspidine proposed for use in this study is not sufficient to elicit a pharmacologic response to the agent. To date, no untoward effects have been attributed to [^{18}F]fluspidine in the ongoing clinical trial; however, it is possible that there are unknown risks with the use of this tracer as it has not been fully characterized at this time.

When using a tracer administered activity of 300±30 MBq per PET session, the radiation exposure due to the cumulative [^{18}F]fluspidine dose for all PET sessions will not exceed 20 mSv which is the maximum specified by the German Radiation Protection Ordinance (Strahlenschutzverordnung §24) for radiation exposure of healthy subjects in medical research. The conversion factor for the effective dose to humans is 22.1 µSv/MBq (Sattler et al 2016; Kranz et al 2016) resulting in an effective dose of 7.3 mSv if the maximum considered activity of 330 MBq (300+10%) would be administered.

A washout period of 7 days will occur between any necessary repeat PET sessions, if applicable.

1.4.3. Known and Potential Benefits and Risks of [^{18}F]fallypride

1.4.3.1. Benefits of [^{18}F]fallypride

[^{18}F]fallypride is a well-characterized high-affinity ligand frequently used in PET studies for the quantification of D2 receptors in the brain; it binds to the D2 receptor with a high specific uptake (Mukherjee et al 1996; Siessmeier et al 2005), making it a suitable PET tracer for use in this study.

There are no direct benefits to the study subject from exposure to [^{18}F]fallypride in this trial.

1.4.3.2. Risks of [^{18}F]fallypride

The mass dose of [^{18}F]fallypride proposed for use in this study is not sufficient to elicit a pharmacologic response to the agent. To date, no untoward effects have been attributed to [^{18}F]fallypride during use as a radiolabeled tracer in PET. Therefore, the risk to subjects exposed to this agent is expected to be minimal.

When using a tracer administered activity of 200±20 MBq per PET session, the radiation exposure due to the cumulative [^{18}F]fallypride dose for all PET sessions will not exceed 20 mSv which is the maximum specified by the German Radiation Protection Ordinance (Strahlenschutzverordnung §24) for radiation exposure of healthy subjects in medical research.

The conversion factor for the effective dose to humans is 21.6 µSv/MBq (Kessler et al 2000) resulting in an effective dose of 4.8 mSv if the maximum considered activity of 220 MBq (200+10%) would be administered.

A washout period of 7 days will occur between any necessary repeat PET sessions, if applicable.

1.4.4. Overall Benefit and Risk Assessment for This Study

This study is intended to demonstrate target engagement, RO of pridopidine to S1R in the brain of healthy subjects and (optional) HD patients.

Single doses of pridopidine will be given to the subjects participating in this study. The starting dose of 90 mg/day was selected for this study because it is the highest single dose that has been given to healthy subjects and is also inclusive of the dose in the ongoing Phase 2 TV7820-CNS-20002 (PRIDE-HD) study in patients with HD. Also, the administration of the tracers and the exposure to them is expected to be minimal.

The results of this study will provide further information and support to pridopidine's proposed mechanism of action in interacting with the D2 and S1R receptors.

The radiation risk by the use [^{18}F]fluspidine and [^{18}F]fallypride is in the order of that by other well established and approved ^{18}F-labeled radioligands for brain PET imaging (Zanotti-Fregonara 2013) and, thus, is justifiable for the intended research purpose.

Based on experience to date with single doses, the highest dose levels selected for this study (90 mg for subjects and 112.5 mg for HD patients) are considered to be safe and well tolerated.

It is therefore the sponsor's belief that the overall benefit and risk assessment for this study is favorable.

1.5. Selection of Drugs and Doses

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

1.5.1. Justification for Dose of Active Drug

[redacted]

1.5.2. Justification for Use of [^{18}F]fluspidine

[^{18}F]fluspidine has demonstrated a high potential for the neuroimaging of S1R brain receptors with PET. Data from preclinical studies and preliminary data from an ongoing initial clinical trial in healthy subjects have demonstrated that [^{18}F]fluspidine binds to the brain receptor with a high specific uptake (Fischer et al 2011; Maisonial et al 2012), making it a suitable PET tracer for use in this study.

1.5.3. Justification for Use of [^{18}F]fallypride

[^{18}F]fallypride is a well-characterized high-affinity ligand frequently used in PET studies for the quantification of D2 receptors in the brain; it binds to the receptor with a high specific uptake (Mukherjee et al 1996; Seissmeier et al 2005), making it a suitable PET tracer for use in this study.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) 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, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

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

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

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

1.7. Study Population and Justification

This study will recruit healthy non-smoking men between 25 and 55 years of age (inclusive) and (optional) men aged ≥25 years with HD. Healthy subjects and HD patients who are poor CYP2D6 metabolizers will be excluded from participation in this study.

Healthy subjects are included so that a relatively homogenous population without significant medical issues can be studied.

HD patients, with neuronal degeneration in the brain, may be included to examine if the results observed in healthy subjects are replicated in patients.

Only men will be enrolled due to safety concerns with women of childbearing potential being exposed to radioactivity and potential effects of corticoid hormones on S1R binding.

1.8. Location and Study Duration

This study is planned to be conducted in Germany at 1 investigational center.

The study is expected to start in Q1 2017 (first subject admission) and be completed in Q1 2018 (last subject last visit).

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

The purpose of this study is to demonstrate engagement of pridopidine with S1R and D2R (optional) in the living human brain and to characterize the exposure-response curve after a single dose administration of pridopidine. No formal statistical analysis will be conducted.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objectives of the study are:

- To demonstrate target engagement, receptor binding/occupancy (RO) of pridopidine to sigma-1 receptors (S1R) in the brain (whole brain, cortical and subcortical regions) of healthy subjects and (optional) Huntington's disease (HD) patients after single oral dose administration;
- To establish the relationship between the plasma pridopidine concentrations and the S1R occupancy in the brain of healthy subjects and (optional) HD patients following a single oral dose of pridopidine.

2.2.2. Secondary Objectives

The secondary objectives of this study are:

- To establish test-retest variability of (S)-(-)-[^{18}F]fluspidine positron emission tomography (PET) imaging of S1R in healthy subjects;
- To evaluate the pharmacokinetics of pridopidine following single oral administration in healthy subjects and (optional) HD patients;
- To assess safety of pridopidine in healthy subjects and (optional) HD patients.

2.2.3. Exploratory Objectives

Exploratory objectives are:

- To explore a potential impact of endogenous corticoid levels on RO of pridopidine to S1R;
- To explore target engagement, RO of pridopidine to the dopamine-2 receptors (D2R) in the brain of healthy subjects and (optional) HD patients;
- To explore the relationship between the plasma pridopidine concentrations and D2R occupancy in the brain of healthy subjects and (optional) HD patients following a single oral dose of pridopidine;
- To establish the relationship between the plasma metabolite TV-45065 concentrations and the S1R occupancy in the brain following a single oral dose of pridopidine to healthy subjects and (optional) HD patients;

- [redacted]

2.3. Study Endpoints

2.3.1. Pharmacodynamic Endpoints

The PET acquisition, as well as advanced magnetic resonance imaging (MRI) protocols (MR-AC, T1 MPRAGE 3D, ASL, 2D MRS, and rs-fMRI) will be detailed in dedicated imaging manuals. These will also contain an analysis plan for the image data. Imaging manuals will be provided prior to initiating the study.

2.3.2. Pharmacokinetic Endpoints

Blood samples for analysis of pridopidine and the metabolite TV-45065 will be obtained up to 24 hours after dosing. Pharmacokinetic parameters to be calculated are detailed in Section 6.1.

2.3.3. Safety and Tolerability Endpoints

The safety and tolerability endpoints are:

- occurrence of adverse events during the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results
- vital signs (blood pressure [BP], respiratory rate, body temperature, and pulse) measurements at each visit
- ECG findings
- physical examination findings, including body weight measurements
- use of concomitant medication during the study

- number (%) of subjects who did not complete the study (end of study)
- number (%) of subjects who did not complete the study due to adverse events

2.3.4. Biomarker Endpoints

Blood samples for biomarker analysis in serum, plasma, and ribonucleic acid (RNA) will be collected up to 24 hours after dosing in visit 3.

2.3.5. Pharmacogenetic Endpoints

A pharmacogenetic blood sample will be collected at screening for genetic analyses of the CYP2D6 metabolizer status and S1R polymorphs.

3. STUDY DESIGN

3.1. General Design and Study Schematic Diagram

This is a Phase 1, single-dose, open-label, adaptive design (S)-(-)-[^{18}F]fluspidine PET study in healthy subjects and (optional) in patients with HD designed to demonstrate target engagement and to assess the occupancy of the S1R by pridopidine. PET with the tracer (S)-(-)-[^{18}F]fluspidine will be used to quantify changes in S1R availability following the administration of pridopidine (Part A). Binding of pridopidine to D2R may be assessed using PET imaging with [^{18}F]fallypride (Part B, optional). Note that this protocol will refer to all study participants (including the HD patients) as 'subjects' except for when specifically referring to the HD patients.

Since endogenous corticoid hormones have been described to competitively bind to S1R (Maurice et al 2006), the test-retest variability of (S)-(-)-[^{18}F]fluspidine PET will be determined in up to 6 healthy subjects in parallel (Part 0). To minimize variability associated with the potential impact of circadian corticoid plasma level changes, individual scan and re-scan sessions will be performed at comparable times of the day for all subjects.

In addition, plasma corticoid levels (to include dehydroepiandrosterone [DHEA], progesterone, testosterone, cortisol, and, where feasible, androstanolone, allopregnanolone, pregnenolone) will be assessed immediately before each (S)-(-)-[^{18}F]fluspidine or [^{18}F]fallypride injection in all subjects.

Pharmacogenetic samples will be collected at screening for CYP2D6 and exploratory genotyping. Biomarker pharmacodynamic samples will be collected at visit 3, prior to dosing and 4, 8, and 24 hours post pridopidine dose (a 10-minute window will be allowed).

Up to 45 subjects are planned to be enrolled in this study to ensure up to 38 evaluable subjects. The study will consist of a screening period of up to 8 weeks prior to first dosing, including a T1 MPRAGE 3D MRI scan (visit 1), a study period of up to 4 weeks (including visits 2 and 3), and a follow-up visit (visit 4). During the study period, the subjects will undergo a baseline PET investigation (PET session 1) at visit 2, and subsequently a post-treatment PET investigation (PET session 2) following a single oral dose of pridopidine at visit 3. Each dose cohort will comprise up to 4 subjects. It is expected that each dose cohort within Part A or Part B will receive a different dose of pridopidine; however, subjects within each cohort will be administered the same dose (deviation will also be allowed). It is possible that subjects in different cohorts within Part A or Part B may receive the same dose of pridopidine if timing of the PET imaging is changed or unchanged (eg, cohort with HD patients).

Subjects in Part A and B may receive the same dose of pridopidine for different tracers or different populations (healthy volunteers or patients with HD). The maximal dose of pridopidine administered will not exceed 90 mg in healthy subjects or 112.5 mg in HD patients (the highest dose investigated in the PRIDE-HD study).

Up to 20 subjects may be evaluated in Part A, although it is expected that study objectives may be achieved with fewer subjects (more subjects will also be allowed). At the day of each PET session, prior to PET imaging, a cubital or forearm vein will be cannulated to inject

(S)-(-)-[^{18}F]fluspidine and (at visit 3 only) to obtain venous blood samples for quantification of pridopidine and its metabolite TV-45065, and also for other exploratory biomarker analysis. The subject's radial artery on the other arm (or the same arm if this cannot be achieved) will be cannulated to obtain arterial blood samples during PET imaging for the quantification of plasma radioactivity associated with (S)-(-)-[^{18}F]fluspidine, in order to estimate a metabolite-corrected arterial plasma input function for PET data analysis.

The PET imaging will consist of subsets of PET scans that will be acquired in list mode: 4 blocks with breaks in between. The first PET acquisition block of 90 minutes duration (0 to 90 minutes) will be started together with the intravenous injection of 300±30 MBq (S)-(-)-[^{18}F]fluspidine; the following acquisition blocks of 30 minutes duration each will be started at 2, 3, and 6 hours post-injection of the PET tracer. Each PET acquisition block will be acquired in list mode in order to allow variable subdivision into multiple time frames as detailed in the imaging manual. In an effort to facilitate easier PET procedure for HD patients after the first 90-minute PET acquisition block, the subsequent 30-minute PET acquisition blocks are made optional per Investigator's judgement (refer to study Imagine Manual for details).

The first dose of pridopidine will be high (90 mg) for subjects enrolled in the first dose cohort but may be changed to another dose based on PRIDE-HD study results. Subsequent doses (0.5 or 1 mg in healthy subjects (Part A only); 2.5, 5, 10, 22.5, 45, or 67.5 mg in healthy subjects and HD patients; and a high dose of 112.5 mg in HD patients) will be determined on the basis of the RO results following PET session 2 and the time-activity profiles of (S)-(-)-[^{18}F]fluspidine from previous cohort subjects. In addition, the timing of the PET sessions may also be revised. If any of the postdose PET investigations are compromised due to technical or logistic reasons, a repeat investigation may be considered, provided that the resulting cumulative radiation exposure by (S)-(-)-[^{18}F]fluspidine for all PET sessions does not exceed the allowed overall study exposure (effective dose not exceeding 20 mSv), when using tracer administered activity of 300±30 MBq per PET session, and further respecting a washout of 7 days of pridopidine and its metabolites. PET session 2 will start at 2 hours postdose of pridopidine.

Up to 15 subjects may be evaluated in Part B to characterize the D2R binding of pridopidine. The cohort structure will also comprise up to 4 subjects. Each of the 2 PET sessions will consist of 4 subsets of acquisition blocks that will be acquired in list mode: 0 to 90 minutes, 120 to 150 minutes, 180 to 210 minutes, and 360 to 390 minutes post-injection of 200±20 MBq [^{18}F]fallypride. Each PET acquisition block will be acquired in list mode in order to allow variable subdivision into multiple time frames, and will be according to the institutional standard as detailed further in the imaging manual. PET session 2 will start at approximately 2 hours postdose of pridopidine. The PET imaging protocol is essentially the same as for (S)-(-)-[^{18}F]fluspidine. From the second block onwards, acquisition can commence within ±10 minutes of the nominal time, but the duration should still be 30 minutes for each of these blocks. In an effort to facilitate easier PET procedure for HD patients after the first 90-minute PET acquisition block, the subsequent 30-minute PET acquisition blocks are made optional per Investigator's judgement.

Brain MRI scans will be performed at screening to ensure subjects are qualified for the study but will also provide data to aid the analysis of PET data. Additional functional MRI scans (MR-AC, T1 MPRAGE 3D, ASL, 2D MRS, and rs-fMRI) will be performed in parallel with the PET

imaging sessions to evaluate the relationship between brain activity and S1R or D2R occupancy by pridopidine. These scans will be further detailed in the imaging manual.

The dose of pridopidine in Part B will be determined based on the results obtained using (S)-(-)-[^{18}F]fluspidine in Part A. The timing of the [^{18}F]fallypride PET scan may also be revised. If any of the postdose PET investigations are compromised due to technical or logistic reasons, a repeat investigation may be considered, provided that the resulting cumulative [^{18}F]fallypride dose for all PET sessions does not exceed the authorized overall study exposure (effective dose not exceeding 20 mSv), when using tracer administered activity of 200±20 MBq per PET session, and further respecting a washout of 7 days of pridopidine and its metabolites.

For the test-retest cohort (Part 0), fluspidine will be administered twice. The 2 tracer doses will be administered separately within a certain time frame, without pridopidine. The PET session 2 will take place at approximately a similar time of day (±1 hour) as the baseline PET session 1, on another day (at least 24 hours ~10 half-lives ^{18}F apart)

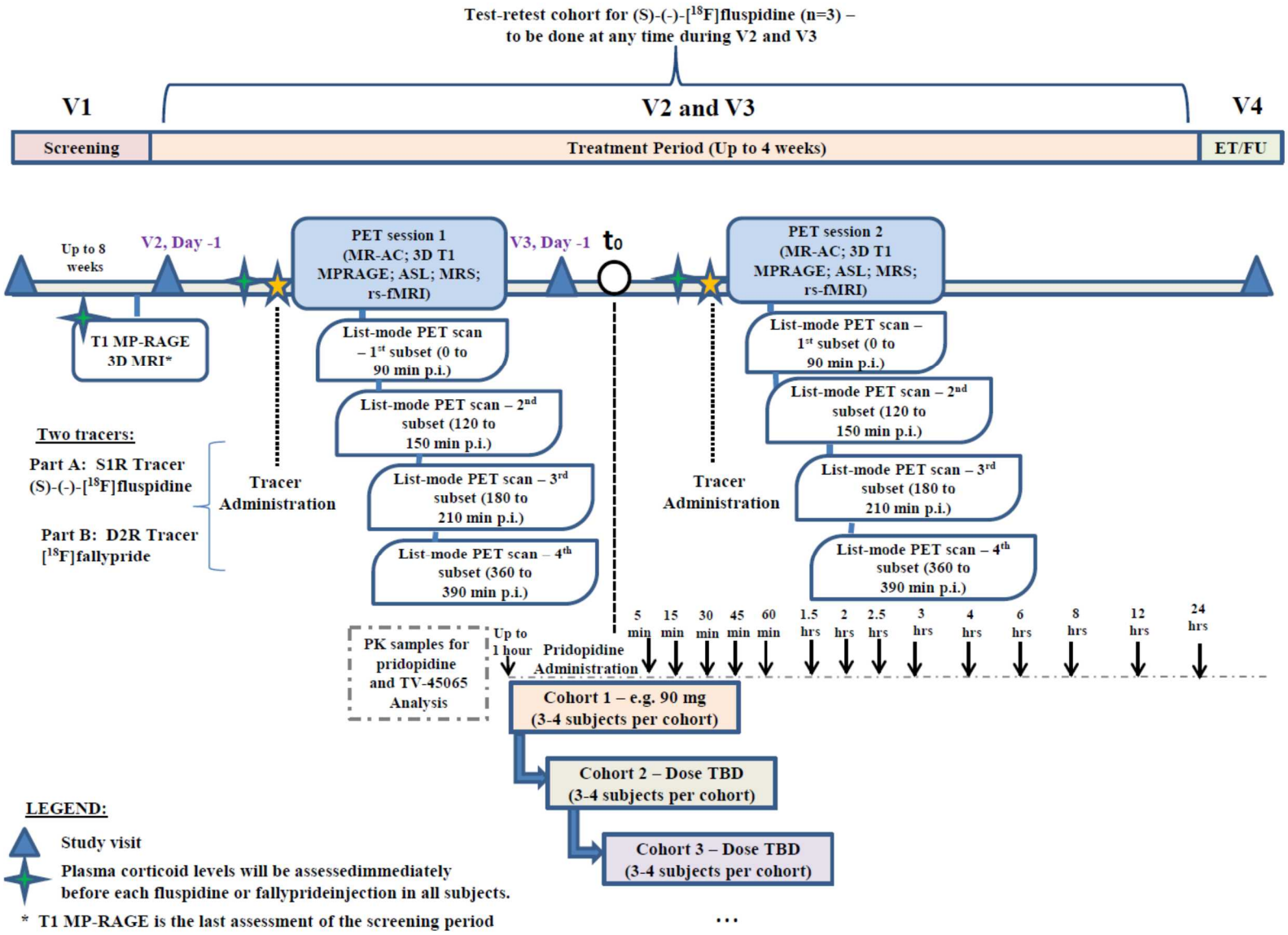
Blood samples for determination of pridopidine and TV-45065 plasma concentrations and exploratory biomarkers will be collected during the timing of the PET examinations in visit 3.

Safety and tolerability (the number [%]) of healthy subjects and HD patients who failed to complete the study due to adverse events) will be assessed throughout the study by monitoring adverse events and by conducting clinical safety laboratory tests, ECG, physical examination, and vital sign assessments.

The assessments and procedures performed during each study visit are detailed in Table 1 and Section 3.14.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



Abbreviations: ASL=Arterial Spin Labeling; 2D MRS=2-dimensional multi-voxel magnetic resonance spectroscopy; D2R=dopamine 2 receptor; ET=Early Termination; FU=follow up; hrs=hours; min=minutes; MR-AC=MRI-based attenuation correction; PET=positron emission tomography; p.i.=post-injection of tracer; rs-fMRI=resting state functional magnetic resonance imaging; S1R=sigma-1 receptor; T1 MPRAGE 3D=T1-weighted rapid 3-dimensional gradient-echo technique; TBD=to be determined;

3.2. Justification for Study Design

The number of subjects studied per dose group is expected to be sufficient to meet the study objectives, which are not based on formal statistical hypothesis. Each dose-group will comprise up to 4 subjects (deviations will be allowed). An additional subject will be added if the results from 1 out of 3 subjects are discordant. It is anticipated that 3 dose levels will be sufficient to characterize the exposure-response profile (deviations will be allowed). However, additional cohorts may be studied. A cohort of HD patients may be added to study engagement of pridopidine to S1R and 2D receptors and to explore the effects of neurodegeneration in patients with HD.

3.3. Pharmacodynamic Measures and Time Points

- PET acquisition up to 390 minutes after injection of the tracer.

3.4. Safety Measures and Time Points

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

- inquiries about adverse events at every visit
- clinical laboratory (serum chemistry, hematology, and urinalysis) tests on day -1 at visits 2 and 3 and at the follow-up (visit 4)
- vital signs (BP, respiratory rate, body temperature, and pulse) measured at every visit
- an ECG recorded at every visit
- physical examinations on day -1 at visits 2 and 3 and at the follow-up (visit 4)
- inquiries about use of concomitant medication at every visit

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

3.5. Pharmacokinetic Measures and Time Points

Blood samples for analysis of pridopidine and the metabolite TV-45065 will be obtained prior to pridopidine dosing (<1 hour), at 5 (±1 minute), 15, 30, 45 and 60 minutes after dosing (±2 minutes), and at 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours after dosing. A 10-minute window will be allowed for all postdose sampling intervals from 1.5 hours up to and including 24 hours after dosing.

A description of the pharmacokinetic parameters is provided in Section 6.1.

3.6. Exploratory Measures and Time Points

The exploratory/other efficacy measures and time points are:

- Endogenous corticoid plasma levels, taken directly prior to tracer dosing
- MR-AC, T1 MPRAGE 3D, ASL, MRS, and rs-fMRI scans in parallel with the PET imaging

- Blood exploratory biomarkers including prolactin, BDNF, monoamines and histamine metabolites up to 24 hours after dosing
- A pharmacogenetic blood sample will be collected at screening for genetic analyses of the CYP2D6 metabolizer status and S1R polymorphs

3.7. Randomization and Blinding

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

3.8. Maintenance of Randomization and Blinding

3.8.1. Maintenance of Randomization

Not applicable.

3.8.2. Blinding/Unblinding

This is an open-label study with no blinding.

3.8.3. Data Monitoring Committee

This study will not be overseen by a Data Monitoring Committee.

3.9. Drugs Used in the Study

3.9.1. Investigational Product - Pridopidine

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

If lower pridopidine doses will be required, it will be prepared on site as follows:

- 0.5 and 1 mg - size 2 capsules will be filled with the appropriate amount of blend taken from the drug product capsules and diluted with [redacted]
- 2.5 mg pridopidine – size 2 capsules will be filled with the appropriate amount of blend taken from the drug product capsules
- 5 and 10 mg pridopidine – size 2 capsules will be filled with the appropriate amount of the active ingredient (neat)

A more detailed description of the preparation of lower doses can be found in the pharmacy manual.

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

This is an uncontrolled study with no other study drug.

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

3.9.2. PET Tracers

3.9.2.1. [^{18}F]fluspidine

The radiolabeled PET tracer [^{18}F]fluspidine for the neuroimaging of S1R receptors with PET will be administered as a single intravenous bolus for each PET scan in Part A of the study, not exceeding 330 MBq and <50 µg mass. (S)-(-)-[^{18}F]fluspidine will be manufactured according to good manufacturing practice (GMP) daily, on an as-needed basis for use in the study, and provided as a clear, colorless, particle free solution consisting of 50 to 4000 MBq/mL (S)-(-)-[^{18}F]fluspidine, 7.5 mL sterile water for injection, 1.5 mL PEG400, 1 mL ethanol, and 0.1 mL of a concentrated sodium phosphate solution. The product will be packaged in TC-Elu-5 multidose containers [redacted]) consisting of a colorless type 1 (Ph. Eur.) glass vessel which is sealed with a gray latex sulfur-free chlorbutyl rubber stopper covered with a blue aluminum and plastic flip-off seal.

The tracer will be labeled containing information regarding the composition of the product.

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

3.9.2.2. [^{18}F]fallypride

The radiolabeled PET tracer [^{18}F]fallypride will be administered as a single intravenous bolus for each PET scan in Part B of the study, not exceeding 220 MBq and <2 µg mass. (S)-(-)-[^{18}F]fallypride will be manufactured according to GMP daily, on an as needed basis, for use in the study and provided as a clear, colorless, particle free solution consisting of 50 to 1000 MBq/mL [^{18}F]fallypride, 9 mL sterile isotonic saline solution for injection, 1 mL ethanol, and 0.1 mL of a concentrated sodium phosphate solution. The product will be packaged in TC-Elu-5 multi-dose containers [redacted] consisting of a colorless type 1 (Ph. Eur.) glass vessel which is sealed with a gray latex sulfur-free chlorbutyl rubber stopper covered with a blue aluminum and plastic flip-off seal.

The tracer will be labeled containing information regarding the composition of the product.

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

3.10. Drug Supply and Accountability

3.10.1. Drug Storage and Security

The study drug (pridopidine) must be stored according to the manufacturer's drug product stipulation, in a dry place, and in a securely locked, substantially constructed cabinet or enclosure.

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

The tracers should be stored shielded, at room temperature (15°C to 25°C/59°F to 77°F).

Only authorized personnel will have access to the study drug. The study site personnel at the site will be responsible for correct storage and handling of the study drug.

3.10.2. Drug Accountability

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

A record of study drug accountability (ie, study drug and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the PI or designee, with an account given for any discrepancies. Empty, partially used, and unused bottles of study drug will be disposed of by the study center according to local procedures.

3.11. Duration of Subject Participation and Justification

Total study duration for each subject is expected to not exceed 12 weeks, with recruitment and screening lasting up to 8 weeks and the study period for each subject lasting up to 4 weeks. Subjects are expected to participate in this study for its entire duration. See Section 12.4 for the definition of the end of study.

3.12. Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (see Section 7.1.5) as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of:

- new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the study drug

A subject may discontinue participation in the study at any time for any reason (eg, withdrawal of consent, adverse event); every effort should be undertaken to find out the reason for discontinuation. The investigator or sponsor can withdraw a subject from the study at any time for any reason (eg, protocol violation or deviation as defined in Section 11.1.2, noncompliance, or adverse event).

3.13. Source Data Recorded on the Case Report Form

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

If data are processed from other institutions or means (eg, clinical laboratory, central image center, or electronic diary data) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data

management) for direct entry into the clinical database (see Section 13.1). All data from other institutions will be available to the investigator.

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

3.14. Study Procedures and Assessments

Study procedures and assessments with their time points are summarized in Table 1. Detailed by-visit information is provided starting with Section 3.14.1. Detailed descriptions of each assessment are provided in Section 6 (pharmacokinetic and pharmacodynamic assessments), Section 7 (safety assessments), and Section 8 (biomarker and pharmacogenetic assessments).

Table 1: Study Procedures and Assessments

Time period	**Up to 8 weeks to 2 weeks before Visit 2**	**Up to 4 weeks**					
Visit number	**Visit 1**	**Visit 2**		**Visit 3**			**Visit 4**
Procedures and assessments	**Screening**[a]	**Day -1 (first admission)**	**Day 1**	**Day -1 (second admission)**	**Day 1**	**Day 2**	**Follow-up**[b]
Informed consent	X						
Medical history[c]	X	X					
Prior medication history[d]	X	X					
Inclusion and exclusion criteria	X	X					
Clinical laboratory tests (hematology, serum chemistry, urinalysis)	X	X		X			X
Coagulation test	X						
Corticoid plasma levels[e]			X		X		
Virology[f]	X						
Urine drug screen	X	X		X			
Physical examination[g]	X	X		X			X
Modified Allen test[h]	X						
UHDRS-TMS (HD patients only)	X	X	X	X	X		
12-lead standard ECG[i]	X	X	X	X	X	X	X
Vital signs measurement[j]	X	X	X	X	X	X	X
C-SSRS (screening version)	X						
Pridopidine administration[k]					X		
(S)-(-)-[^{18}F]fluspidine or [^{18}F]fallypride administration[l]			X		X		
Screening T1 MPRAGE 3D MRI[m]	X						
PET scan for test-retest cohort[n]			X		X		
PET session 1[o]			X				
PET session 2[p]					X		

Time period	**Up to 8 weeks to 2 weeks before Visit 2**	**Up to 4 weeks**					
Visit number	**Visit 1**	**Visit 2**		**Visit 3**			**Visit 4**
Procedures and assessments	**Screening**[a]	**Day -1 (first admission)**	**Day 1**	**Day -1 (second admission)**	**Day 1**	**Day 2**	**Follow-up**[b]
MR-AC, T1 MPRAGE 3D MRI, ASL, 2DMRS, rs-fMRI			X[q]		X[p]		
Blood samples for radioactivity levels[r]			X		X		
Blood samples for PK analyses[s]					X	X	
Blood samples for PD biomarker analysis[t]				X	X	X	
Genotyping for CYP2D6 and exploratory[u]	X						
Monitoring of adverse events[v]	X	X	X	X	X	X	X
Concomitant medication[w]	X	X	X	X	X	X	X
Check of study compliance		X		X			

[a] The screening procedures can be performed over several days as long as they are completed within the defined visit window. During screening, subjects will be informed of study restrictions and compliance requirements.

[b] The follow-up visit will take place 6 days after the visit 3 dose (±1 day).

[c] Events that occurred prior to the signing of the informed consent form will be recorded in the medical history.

[d] Medications administered prior to any study drug administration will be recorded as prior medications.

[e] Corticoid plasma levels, to be taken directly prior to tracer dosing (DHEA, progesterone, testosterone, cortisol, where feasible also androstanolone, allopregnanolone, pregnenolone).

[f] Virology testing will include: human immunodeficiency virus (HIV-1, HIV 2), HBsAg, and/or hepatitis C.

[g] Height, weight, and body mass index will be measured only at screening. Complete physical examination on screening and follow up/early termination visits only. On other occasions, abbreviated/symptom- oriented physical examination will be conducted.

[h] Part 0 and Part A subjects only.

[i] The 12-lead ECG is to be performed before pridopidine administration; immediately before administration of the tracer (approximately 90 minutes after pridopidine administration), and at the end of the first PET scan (approximately 3.5 hours after pridopidine administration). When ECG collection coincides with a pharmacokinetic sample, ECG will be collected before the pharmacokinetic sample.

[j] Vital signs (pulse, respiratory rate, body temperature, and systolic and diastolic BP) will be measured with the subject seated or supine immediately prior to administration of pridopidine, and prior to and immediately after each PET scan. BP will be measured in the same arm throughout the study, whenever possible. When vital signs collection coincides with PK sample, vital signs will be collected before the PK sample.

[k] Except for test-retest cohort (Part 0).

[l] [^{18F}]fluspidine for Parts A and 0, [^{18F}]fallypride administration for Part B.

[m] This should be performed as the final procedure of the screening visit, after all other eligibility criteria have been fulfilled.

[n] For the test-retest cohort, fluspidine will be administered twice. The 2 tracer doses will be administered separately within a certain time frame, without pridopidine. The PET session 2 will take place at approximately a similar time of day (±1 hour) as the baseline PET session 1, on another day (at least 24 hours ~10 half-lives ^{18}F apart).

[o] In an effort to facilitate easier PET procedure for HD patients, after the first 90-minute PET acquisition block, the subsequent 30-minute PET acquisition blocks are made optional per Investigator's judgement (refer to study Imaging Manual for details).

[p] The PET session 2 will take place at approximately a similar time of day (±1 hour) as the baseline PET session 1, on another day (per PET slots scheduling availability). It will begin approximately 2 hours after pridopidine administration. The complete scan duration is 3 hours for both fluspidine and fallypride with breaks. Note: In an effort to facilitate easier PET procedure for HD patients, after the first 90-minute PET acquisition block, the subsequent 30-minute PET acquisition blocks are made optional per Investigator's judgement (refer to study Imaging Manual for details).

[q] These should be done simultaneously to the dynamic list-mode PET scans.

[r] Arterial blood samples for radioactivity levels will be obtained after administration of (S)-(-)-[^{18}F]fluspidine; a total of 51 samples (43 × 2 mL and 8 × 10 mL) will be collected at 39 time points during 210 minutes after injection of the tracer. Note: samples will not be collected for Part B.

[s] Blood samples for analysis of pridopidine and the metabolite TV-45065 will be obtained prior to pridopidine dosing (<1 hour) at 5 (±1 minute), 15, 30, 45 and 60 minutes after dosing (±2 minutes), and at 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours after dosing. A 10-minute window will be allowed for all postdose sampling intervals from 1.5 hours up to and including 24 hours after dosing. Note: samples will not be collected for Part 0

[t] At visit 3, blood will be collected for exploratory biomarker analysis on day -1 and on days 1 and 2 (prior to treatment, and at 4, 8, and 24 hours postdose; a 10-minute window will be allowed). For Part 0 where no treatment is given the time points corresponds to 2 hours prior to and 2, 6, and 22 hours post tracer injection.

[u] Blood sampling for pharmacogenetics can be performed at a separate visit within the screening period after informed consent is obtained. Remnant sample will be retained for future exploratory analysis.

[v] Adverse events inquiry and concomitant medication review will occur throughout the study. The period for adverse event reporting is defined as the time period from signing of the informed consent form through the end of the follow-up period. Conditions that worsen or events that occur after signing of informed consent will be recorded as an adverse event.

[w] Medications administered following the first dose and throughout the study will be recorded as concomitant medication.

Abbreviations: ASL=arterial spin labeling; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP2D6=cytochrome P450 2D6; DHEA=dehydroepiandrosterone; 2DMRS=two dimensional multi-voxel magnetic resonance spectroscopy; ECG=electrocardiography; HBsAg=hepatitis B surface antigen; HD=Huntington's disease; HIV=human immunodeficiency virus; MR-AC=MRI-based attenuation correction; MRI=magnetic resonance imaging; PD=pharmacodynamic; PET=positron emission tomography; PK=pharmacokinetics; rs-fMRI=resting state functional magnetic resonance imaging; T1 MPRAGE 3D=T1-weighted rapid 3-dimensional gradient-echo technique; UHDRS-TMS=Unified Huntington's Disease Rating Scale – Total Motor Score

3.14.1. Procedures for Screening and Enrollment (Visit 1)

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

After informed consent is obtained, subjects who are screened will be assigned an 8-digit permanent identification number such that all subjects 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 assigned number of the investigational center, and the last 3 digits will be assigned at the investigational center (eg, if the number assigned to the country is 01, the 3rd subject screened at 5th investigational center would be given the number of 01005003).

A subject who is screened but not enrolled, eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time, may be considered for screening again if, eg, there is a change in the subject's medical background or a modification of study inclusion and exclusion criteria.

The screening visit (visit 1) will take place between 8 and 2 weeks before visit 2. The following procedures will be performed at visit 1:

- obtain written informed consent before any study-related procedures are performed
- review medical history
- review prior medication history
- review inclusion and exclusion criteria
- clinical laboratory tests (hematology, serum chemistry, urinalysis, and coagulation)
- virology testing for human immunodeficiency virus (HIV-1, HIV-2), hepatitis B surface antigen (HBsAg) and/or hepatitis C
- urine drug screen
- full physical examination (including height and weight)
- modified Allen test for both hands (except for Part B subjects)
- UHDRS-TMS (HD patients only)
- 12-lead standard ECG
- vital signs measurements
- Columbia-Suicide Severity Rating Scale (C-SSRS, screening version)
- genotyping for CYP2D6 metabolism status and storage of deoxyribonucleic acid (DNA) remnant for S1R and exploratory genotyping

- genotyping for cytosine-adenosine-guanine (CAG) (HD patients only)
- concomitant medication review
- monitoring for adverse events (post informed consent form signature)
- inform subjects of study restrictions and compliance requirements
- T1 MPRAGE 3D MRI (this should be performed as the final procedure of the screening visit, after all other eligibility criteria have been fulfilled)

3.14.2. Visit 2 (PET Session 1)

Subjects who meet the inclusion and exclusion criteria at visit 1 will continue to visit 2.

Subjects who continue to meet the inclusion and exclusion criteria will be assigned a permanent unique treatment number. This assigned number will be entered in the CRF.

3.14.2.1. Visit 2, Day -1

The following procedures will be performed at visit 2, day -1:

- review of medical history
- review of prior medication history
- review inclusion and exclusion criteria
- clinical laboratory testing (hematology, serum chemistry, and urinalysis)
- urine drug screen
- abbreviated/symptom-oriented physical examination
- UHDRS-TMS (HD patients only)
- 12-lead standard ECG
- vital signs measurements
- inquire about adverse events
- review of concomitant medication
- review study compliance

3.14.2.2. Visit 2, Day 1

The following procedures will be performed at visit 2, day 1:

- corticoid plasma level measurements
- UHDRS-TMS (HD patients only)
- 12-lead standard ECG
- vital signs measurements
- [^{18}F]fluspidine (Parts A and 0) or [^{18}F]fallypride (Part B) administration – refer to study Imaging Manual for details

- PET scan (session 1) - refer to study Imaging Manual for details
- MR-AC, T1 MPRAGE 3D, ASL, 2DMRS, and rs-fMRI – refer to study Imaging Manual for details
- collect blood samples for measurement of radioactivity levels (excluding Part B subjects) – refer to study Imaging Manual for details
- inquire about adverse events
- review of concomitant medication

3.14.3. Visit 3 (PET Session 2)

3.14.3.1. Visit 3, Day -1

The following procedures will be performed at visit 3, day -1:

- clinical laboratory testing (hematology, serum chemistry, and urinalysis)
- urine drug screen
- abbreviated/symptom-oriented physical examination
- UHDRS-TMS (HD patients only)
- 12-lead standard ECG
- vital signs measurements
- inquire about adverse events
- review of concomitant medication
- review study compliance
- collection of blood for exploratory pharmacodynamic biomarker analysis

3.14.3.2. Visit 3, Day 1

The following procedures/assessments will be performed at visit 3, day 1:

- corticoid plasma level measurements
- UHDRS-TMS (HD patients only)
- 12-lead standard ECG
- vital sign measurements
- pridopidine administration
- [^{18}F]fluspidine (Parts A and 0) or [^{18}F]fallypride (Part B) administration – refer to study Imaging Manual for details
- PET scan (session 2) – refer to study Imaging Manual for details
- MR-AC, T1 MPRAGE 3D, ASL, 2DMRS, and rs-fMRI – refer to study Imaging Manual for details

- collect blood samples for measurement of radioactivity levels (excluding Part B subjects) – refer to study Imaging Manual for details
- collect blood samples for pharmacokinetic analyses (predose and up to 12 hours after dosing)
- collect blood samples for exploratory pharmacodynamic biomarker analysis (predose and 4 and 8 hours postdose)
- monitoring of adverse events
- review of concomitant medication

3.14.3.3. Visit 3, Day 2

The following procedures/assessments will be performed at visit 3, day 2:

- 12-lead standard ECG
- vital signs measurements
- collect blood samples for pharmacokinetic analyses (24 hours postdose)
- collect blood samples for exploratory pharmacodynamic biomarker analysis (24 hours postdose)
- monitoring of adverse events
- review of concomitant medications

3.14.4. Procedures After Study Drug Treatment (Visit 4)

For subjects who complete the study or withdraw prematurely, final evaluations will be performed at visit 4, which will take place 6 days after the visit 3 dose (±1 day). The following procedures are to be performed at visit 4:

- clinical laboratory testing (hematology, serum chemistry, and urinalysis)
- full physical examination
- 12-lead standard ECG
- vital signs measurements
- monitoring of adverse events
- review of concomitant medications

Procedures for subjects who withdraw prematurely from the study are described in Section 4.4

Subjects with ongoing adverse events will be monitored as described in Section 7.1.2. Otherwise, the follow-up visit will be the last study visit.

3.14.5. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the subject's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be

recorded on the CRF as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

Procedures performed during unscheduled visits include the following:

- concomitant medication inquiry
- vital signs measurements
- adverse event inquiry

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

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow subjects to be enrolled are not granted by Teva (see Section 11.1.2).

4.1. Subject Inclusion Criteria

Subjects may be enrolled in this study only if they meet all of the following criteria:

Healthy Subjects:

a. Male subjects between 25 and 55 years (inclusive) of age, with a body mass index (BMI) ≥18.0 to ≤30 kg/m^2 and a body weight of at least 50 kg (inclusive).

b. In general, good physical and mental health as determined by medical history and psychiatric history, suicidality assessment, physical examination, 12-lead ECG, vital signs, and clinical laboratory tests. A subject with a clinical abnormality in the laboratory profile or BP can be included only if the investigator or his designee considers that the abnormality does not introduce an additional risk factor for the subject's health, or interfere with the study objectives.

c. Men who are potentially fertile (not surgically [eg, vasectomy] or congenitally sterile), whose female partners are of childbearing potential, must use contraception for the duration of the study and for 90 days after discontinuation of study drug (because of the possible effects on spermatogenesis). Highly effective methods of contraception are those with a failure rate of less than 1% per year (eg, female partner's use of hormonal contraceptive [oral, implanted, transdermal, injected], female partner's use of an intrauterine device [IUD]), and barrier method with spermicide. In addition, male subjects may not donate sperm for the duration of the study and for 90 days after discontinuation of study drug.

d. Are able to understand the requirements of the study; are willing to comply with the requirements of the study (eg, imaging procedures, all dietary, exercise, and alcohol restrictions) and provided their written informed consent to participate in the study.

e. Willing to provide a blood sample for genetic analyses (including CYP2D6 status, S1R polymorphs, genetic long QT syndrome in patients who had QT prolongation following study drug administration or any other genetic analyses related to pridopidine response) at the screening visit.

Patients with Huntington's disease:

a. Diagnosis of HD based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene.

b. Male age ≥25 years, with an onset of HD after 18 years of age.

c. Men who are potentially fertile (not surgically [eg, vasectomy] or congenitally sterile), whose female partners are of childbearing potential, must use contraception for the duration of the study and for 90 days after discontinuation of study drug (because of the possible effects on spermatogenesis). Highly effective methods of

contraception are those with a failure rate of less than 1% per year (eg, female partner's use of hormonal contraceptive [oral, implanted, transdermal, injected], female partner's use of an IUD), and barrier method with spermicide. In addition, male patients may not donate sperm for the duration of the study and for 90 days after discontinuation of study drug.

d. Body weight ≥50 kg.

e. A sum of ≥25 points on the UHDRS-TMS at the screening visit.

f. 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.

g. Willing to provide a blood sample for genetic analyses (including CAG analysis, CYP2D6 status, S1R polymorphs, 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.

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

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

j. Availability and willingness of a caregiver, informant or family member to accompany the patient to the clinic at study visits. The suitability of the caregiver should be judged by the investigator.

k. 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 (visit 2, day -1) and must be kept constant during the study.

l. Are able to understand the requirements of the study; are willing to comply with the requirements of the study (eg, imaging procedures, all restrictions) and provided their written informed consent to participate in the study.

4.2. Subject Exclusion Criteria

Subjects will not be enrolled in this study if they meet any of the following criteria:

Healthy Subjects:

a. CYP2D6 poor metabolizers

b. The subject has been previously exposed to ionizing radiation or radioactive substances as a result of clinical research or medical treatment in the past 10 years.

c. The subject has large scale tattoos, in particular involving the head and neck area.

d. The subject has a counterindication to having an MRI, including (but not limited to):

   – The presence of metal implants (excluding metal dental crowns) that could affect MRI imaging OR

- has worked with ferrous metals either as a vocation or hobby (for example sheet metal worker, welder or machinist) in such a way that might have led to unknown indwelling of metal fragments that could cause injury if moved in response to the magnetic fields during the MRI imaging.

e. The subject suffers from claustrophobia or needle phobia.

f. The subject has a finding on screening MRI that will, in the opinion of the PI impair the safety of the subject or the scientific integrity of the study.

g. The subject has a known coagulation abnormality.

h. Parts A and 0 only: Individuals who had evidence of only one patent arterial supply to the hand (modified Allen test).

i. Any current or history of heart condition or increased pro-arrhythmic risk, including:

- History of cardiovascular disease (eg, coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension, deep vein thrombosis, pulmonary embolism, family history of thrombophilia)
- History of Long QT Syndrome or a first degree relative with this condition
- Family history of sudden death/Brugada syndrome
- A prolonged Fridericia-corrected QT (QTcF) interval (defined as a QTcF interval of >450 msec) at the screening or admission (baseline) visit(s). If there is evidence of a prolonged QTcF interval from the initial (single) measurement, then the ECG can be repeated twice, and the mean of the 3 screening measurements will be used to determine whether or not the subject is suitable for inclusion in the study.
- Any repolarization deficits
- Untreated hypokalemia and/or untreated hypomagnesaemia
- Unclear syncopes
- Any other clinically significant abnormal ECG as judged by the investigator.

j. Creatinine clearance <90 mL/min at screening, calculated using the Cockcroft-Gault equation. It is permitted to repeat the test once, if clinically appropriate.

k. Hemoglobin value below the lower limit of the reference range and evaluated by the investigator to be clinically significant.

l. Positive serology for HIV-1, HIV-2, HBsAg, and/or hepatitis C.

m. Presents or has a history of clinically significant diseases of the renal, hepatic, gastrointestinal, cardiovascular, musculoskeletal, immunological, endocrine (including diabetes even if controlled by diet), metabolic diseases, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs, as judged by the investigator.

n. History of alcohol, narcotic, or any other substance dependence in the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013).

o. History of clinically significant psychiatric diseases, such as major depressive disorder or anxiety, as judged by the investigator.

p. Subjects with adverse events of suicidal ideation or attempt at any time in the past or as measured by suicide ideation score of ≥3 on the C-SSRS (screening version), or subjects who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) if the attempt or acts were performed at any time in the past, or subjects who, in the opinion of the investigator, present a risk of suicide.

q. Has had one of the following conditions:

- major trauma or surgery in the 2 months before screening or at any time between screening and admission
- acute/chronic infection within 2 weeks before screening or at any time between screening and admission
- malignancy within the last 5 years
- epilepsy, seizure, convulsions or syncope (including febrile seizures)
- history of tuberculosis
- BP outside the range of 90 to 139 mmHg (systolic) or 55 to 89 mmHg (diastolic); or pulse rate outside the range of 45 to 99 bpm; all measured after 5 minutes rest in seated or supine position. Vital signs may be retested twice at intervals of 5 minutes.

r. Not willing or able to refrain from intensive physical exercise during the study.

s. Current or history of clinically significant allergy or known hypersensitivity to any ingredients of the study medication [redacted]

t. Planned medical treatments (excluding dental care) during the study period, which may interfere with the study.

u. Use of one of the following prohibited drugs, substances, or foods as follows:

- an investigational drug (new chemical entity) within 6 weeks prior to the first day of study drug administration or within 5 half-lives (whichever is longer)
- any monoamine oxidase inhibitors within 14 days before the first day of study drug administration
- any other medications (including over-the-counter [OTC] medications, vitamins, or herbal or nutritional supplements) within 7 days before the first day of study drug administration (except paracetamol/acetaminophen or ibuprofen used occasionally, up to 24 hours before the first day of study drug administration)

- drugs known to significantly inhibit CYP2D6 enzyme drug metabolism within 21 days prior to the first day of study drug administration or within 5 half-lives (whichever is longer) before the first day of study drug administration, or drugs known to significantly induce CYP enzyme drug metabolism within 28 days before the first day of study drug administration
- drugs known to cause significant QT-prolongation such as anti-arrhythmic drugs or antidepressants within 28 days before the first day of study drug administration
- daily consumption of more than 6 units of caffeine and/or xanthine-containing products, within 2 weeks before the first dose of study drug, or not able to refrain from consumption of more than 2 units of caffeine-containing foods or drinks from 48 hours prior to admission visit and discharge. One caffeine unit is contained in the following items: 1 cup of coffee, 2 cans of cola, 1 cup of tea, ½ cup of energy drink (eg, Red Bull) or 3 chocolate bars. Subject should be able to abstain from caffeine intake for 20 hours during any day.
- cigarette smoking (defined as >5 cigarettes per week) or use of other nicotine-containing products (eg, snuff, nicotine patch, nicotine chewing gum, mock cigarettes, or inhalers). Ex-smokers should have ceased smoking at least 6 months before screening.
- any food or drink/beverage containing alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, brussel sprouts, mustard), and charbroiled meats within 7 days before the first day of study drug administration until after the last day of pharmacokinetic sampling.
- a positive urine drug test or a positive alcohol breath analyzer test at admission visits, or not willing or able to refrain from illicit drugs during the study.

v. Donation or reception of any blood products (eg, plasma, platelets, etc) in the 1 month before the first day of study drug administration, or has made more than 2 donations within the 12 months preceding the first day of study drug administration, or plans to donate during the study or during the 1 months after the last study visit.

w. The subjects cannot participate or successfully complete the study, in the opinion of the investigator, for any of the following reasons:

- The subject is mentally or legally incapacitated, or unable to give consent for any reason.
- The subject is in custody due to an administrative or a legal decision, or under tutelage, or being admitted to a sanitarium or social institution.
- The subject is unable to be contacted in case of emergency.
- The subject is an employee of the site or a relative of an employee at the site.
- Any other reason, at the discretion of the investigator.

Patients with Huntington's disease:

a. CYP2D6 poor metabolizers

b. The patient has been previously exposed to ionizing radiation or radioactive substances as a result of clinical research or medical treatment in the past 10 years.

c. The patient has large scale tattoos, in particular involving the head and neck area.

d. The patient has a counterindication to having an MRI, including (but not limited to):

   – The presence of metal implants (excluding metal dental crowns) that could affect MRI imaging OR

   – has worked with ferrous metals either as a vocation or hobby (for example sheet metal worker, welder or machinist) in such a way that might have led to unknown indwelling of metal fragments that could cause injury if moved in response to the magnetic fields during the MRI imaging.

e. The patient suffers from claustrophobia or needle phobia.

f. The patient has a finding on screening MRI that will, in the opinion of the PI impair the safety of the subject or the scientific integrity of the study.

g. The patient has a severe motor impairment that might cause artifacts.

h. The patient has an known coagulation abnormality.

i. Parts A and 0 only: Individuals who had evidence of only one patent arterial supply to the hand (modified Allen test).

j. 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.

k. 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 first admission, 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, (iv) history of deep vein thrombosis or pulmonary embolism, and/or (v) family history of thrombophilia.

l. Patients with a known history of Long QT Syndrome or a first degree relative with this condition.

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

n. 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, endocrine [including controlled diabetes], gastrointestinal, and metabolic diseases) 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.

o. 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.

p. Patients receiving medications (within the last 6 weeks prior to baseline [visit 2, day -1]) 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.

q. Patients receiving medications (within the last 6 weeks prior to baseline [visit 2, day -1]) that are metabolized by CYP2D6 and have the potential of reducing seizure threshold.

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

s. 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 enters the study.

t. Alcohol and/or drug abuse within the 6 months prior to screening, as defined by DSM-5 (American Psychiatric Association 2013).

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

v. Patients with known intracranial neoplasms, vascular malformations, history of cerebrovascular accident, or intracranial hemorrhage.

w. Current or history of clinically significant allergy or known hypersensitivity to any ingredients of the study medication [redacted]

x. Treatment with tetrabenazine within 6 weeks of study baseline (visit 2, day -1).

y. Treatment with any investigational product within 6 weeks of screening prior to the first day of study drug administration or within 5 half-lives (whichever is longer) or

patients planning to participate in another clinical study assessing any investigational product during the study.

z. Use of one of the following prohibited substances, or foods as follows:
   - any food or drink/beverage containing alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, brussel sprouts, mustard), and charbroiled meats within 7 days before the first day of study drug administration until after the last day of pharmacokinetic sampling.
   - a positive urine drug test or positive alcohol breath analyzer test at admission visits, or not willing or able to refrain from illicit drugs during the study.

aa. Positive serology for HIV-1, HIV-2, HBsAg, and/or hepatitis C.

4.3. Justification for Key Inclusion and Exclusion Criteria

The majority of participants enrolled in this study will be healthy subjects; therefore, the inclusion/exclusion criteria established for this trial are those typically utilized to define this population. Due to unknown potential effects of the ^{18}F-tracers on a developing fetus, women have been excluded from participation in the trial, and male subjects must agree to use contraception for the duration of the trial and for 90 days after discontinuation of the study drug. [redacted], subjects with current or history of a heart condition or increased pro-arrhythmic risk, epilepsy or seizures within the last 5 years, and clinically significant psychiatric diseases such as major depressive disorder or anxiety are to be excluded from participation in this study.

All subjects participating in this study will receive multiple scans (MRI and PET); therefore, individuals with a history of claustrophobia will be excluded from participation in this study. Additionally, subjects may not have counterindications to MRI such as the presence of metal implants, exposure to ferrous metals either as a vocation or hobby in such a way that unknown embedded metal fragments may cause injury to the subject during exposure to the magnetic field generated during imaging.

Since all subjects will be receiving 2 applications of the radioactive tracer resulting in more than 10 mSv effective dose as part of this study, all subjects must not have been exposed to ionizing radiation as a result of research or radiation treatment procedures during the previous 10 years (§88(2) German Radiation Protection Act), excluding diagnostic procedures (eg, computed tomography).

[redacted] and to ensure a reasonable minimum clearance in all subjects through the renal pathway, subjects with a creatinine clearance (calculated by the Cockcroft-Gault formula) <90 mL/min and HD patients with creatinine clearance <60 mL/min will be excluded from the study.

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

4.4. Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of intercurrent illness, adverse events, or other reasons concerning the health or well-being of the subject, or in the event of lack of cooperation. In addition, a subject may be withdrawn from the study drug treatment as described in Sections 3.12, 3.14.4, and 7.1.7.

Should a subject decide to withdraw after administration of study drug(s), or should the investigator decide to withdraw the subject, 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 subject's withdrawal should be made and an explanation given as to why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from study drug treatment and the reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed to the CRF. If a subject withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event 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 subject is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event or test result must be recorded on the source documentation and transcribed to the CRF.

5. TREATMENT OF SUBJECTS

5.1. Drugs Administered During the Study

5.1.1. Pridopidine

In this study, pridopidine can be administered as 0.5 or 1 mg in healthy subjects (Part A only); 2.5, 5, 10, 22.5, 45, 67.5, or 90 mg in healthy subjects and HD patients; and a higher dose of 112.5 mg may also be administered to HD patients. The applicable dose will be given selecting the lowest possible number of capsules. Pridopidine will be administered orally with 240 mL of water.

Study drug will be packaged in bottles and will be provided to the site for administration to subjects (see Section 3.9).

Lower dose study drugs will be packed in bottles on site (1 bottle per patient), prior to administration to the subjects.

5.1.2. [^{18}F]fluspidine

The radiolabeled PET tracer [^{18}F]fluspidine will be provided as a sterile, clear, colorless particle free solution to be administered intravenously for the neuroimaging of S1R brain receptors. The label on the tracer delivered for use in the PET scans will contain information regarding the composition of the product.

During the study period, the subjects will undergo a baseline PET investigation (PET session 1) and a post-treatment PET investigation during the study period (PET session 2) following a single oral dose of the study drug, pridopidine. On the day of each PET session, prior to PET imaging, a cubital or forearm vein will be cannulated to inject (S)-(-)-[^{18}F]fluspidine (300±30 MBq) and, at visit 3, to obtain venous blood samples for quantification of pridopidine and its metabolite TV-45065 and other exploratory biomarker analysis. The subject's radial artery on the other arm (or the same arm if this cannot be achieved) will be cannulated to obtain arterial blood samples during PET imaging for the quantification of plasma radioactivity associated with (S)-(-)-[^{18}F]fluspidine, in order to estimate a metabolite-corrected arterial plasma input function for PET data analysis. A total of 51 samples (43 × 2 mL and 8 × 10 mL) will be collected at 39 time points during 210 minutes after injection of the tracer. The arterial sampling intervals will be according to the institutional standards, as detailed in the study imaging manual.

If any of the postdose PET investigations are compromised due to technical or logistic reasons, a repeat investigation may be considered, provided that the resulting cumulative (S)-(-)-[^{18}F]fluspidine dose for all PET sessions does not exceed the authorized overall study exposure (effective dose not exceeding 20 mSv), when using tracer administered activity of 300±30 MBq per PET session, and further respecting a washout of 7 days of pridopidine and its metabolites.

5.1.3. [^{18}F]fallypride

The radiolabeled PET tracer [^{18}F]fallypride will be provided as a sterile clear colorless particle free solution to be administered intravenously for the neuroimaging of D2 receptors in the brain.

The label on the tracer delivered for use in the PET scans will contain information regarding the composition of the product.

During the study period, the subjects will undergo a baseline PET investigation (PET session 1) and a post-treatment PET investigation during the study period (PET session 2) following a single oral dose of the study drug, pridopidine. On the day of each PET session, prior to PET imaging, a cubital or forearm vein will be cannulated to inject [^{18}F]fallypride (200±20 MBq) and, at visit 3, to obtain venous blood samples for quantification of pridopidine and its metabolite TV-45065 and other exploratory biomarker analysis.

If any of the postdose PET investigations are compromised due to technical or logistic reasons, a repeat investigation may be considered, provided that the resulting cumulative [^{18}F]fallypride dose for all PET sessions does not exceed the authorized overall study exposure (effective dose not exceeding 20 mSv), when using tracer administered activity of 200±20 MBq per PET session, and further respecting a washout of 7 days of pridopidine and its metabolites.

5.2. Restrictions

Medications prohibited before and/or during the study are described in Section 5.3. Restrictions in regard to birth control and required laboratory values are provided in the inclusion and exclusion criteria.

Healthy subjects will be required to comply with the following additional restrictions:

- Activity
  - Subjects must remain seated or supine for safety reasons during the pridopidine administration and for 1 hour after each pridopidine administration. Subjects will be allowed to use the restroom (escorted by investigational center staff) during this time, as needed.
  - Subjects will be asked to maintain normal physical activity from at least 5 days before the start of the study.
  - Subjects are not to engage in strenuous exercise during the inpatient periods of this study.
- Fasting
  - Subjects will fast from waking; a light breakfast (without caffeine) is allowed, to be completed at least 2 hours before drug administration.
- Specific food, beverages, etc
  - Subjects may not consume any food or drink/beverage containing alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, brussel sprouts, mustard), and charbroiled meats within 7 days before the first day of study drug administration until after the last day of pharmacokinetic sampling.
  - Daily consumption of more than 6 units of caffeine and/or xanthine-containing products will be prohibited for a minimum of 2 weeks before the first dose of study drug. One caffeine unit is contained in the following items: 1 cup of coffee,

2 cans of cola, 1 cup of tea, ½ cup of energy drink (eg, Red Bull), or 3 chocolate bars. Consumption of such products will be restricted to no more than 2 units of caffeine-containing foods or drinks from 48 hours prior to admission visit and discharge. Subject should be able to abstain from caffeine intake for 20 hours during any day. Caffeine must not be consumed after 1800 hours on day -1 at visits 2 and 3, and should not be provided with breakfast on day 1 of visits 2 and 3.

- Subjects must not donate any blood products (eg, plasma, platelets, etc) during the study or during the 1 month after the last study visit.
- Smoking >5 cigarettes per week is not permitted during the study.

Patients will be required to comply with the following additional restrictions to the best of their ability:

- Activity
  - Patients must remain seated or supine for safety reasons during the pridopidine administration and for 1 hour after each pridopidine administration. Patients will be allowed to use the restroom (escorted by investigational center staff) during this time, as needed.
- Fasting
  - Patients will fast from waking; a light breakfast (without caffeine) is allowed, to be completed at least 2 hours before drug administration.
- Specific food, beverages, etc
  - Patients may not consume any food or drink/beverage containing alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, brussel sprouts, mustard), and charbroiled meats within 7 days before the first day of study drug administration until after the last day of pharmacokinetic sampling.
  - Caffeine must not be consumed after 1800 hours on day -1 at visits 2 and 3, and should not be provided with breakfast on day 1 of visits 2 and 3.
- Patients must not donate any blood products (eg, plasma, platelets, etc) during the study or during the 1 month after the last study visit.

5.3. Prior and Concomitant Medication or Treatment

Medications administered prior to any study drug administration will be recorded as prior medications and medications administered following the first dose and throughout the study will be recorded as concomitant medication. Any prior or concomitant therapy, medication, or procedure a subject has had within 28 days before study drug administration and up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, dosage, and dosing start and stop times will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary (WHO Drug).

For healthy subjects, other than study drug, no drug is allowed during the study, except for the occasional use of paracetamol/acetaminophen or ibuprofen. Prohibited medication for HD patients is detailed in Section 5.3.1.

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

5.3.1. Prohibited Medication for HD Patients

5.3.1.1. 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 2, day -1) and during the study.

5.3.1.2. 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 2, day -1) and during the study.

5.3.1.3. Antiarrhythmic Medication

Disopyramide, procainamide, quinidine, flecainide, propafenone, amiodarone, dofetilide, ibutilide, and sotalol are not allowed within 6 weeks of baseline (visit 2, day -1) and during the study.

5.3.1.4. Medications Lowering Seizure Thresholds

Maprotiline, dipipanone, dihydrocodeine, methadone, oxycodone, papaveretum, pentazocine, and tramadol are not allowed within 6 weeks of baseline (visit 2, day -1) and during the study

5.3.1.5. Medications Interfering with Blood Coagulation

The following medications are not allowed within 6 weeks of baseline (visit 2, day -1) and during the study (except if required to treat adverse events):

- Drugs which inhibit platelet function (antithrombic drugs) – aspirin, dipyridamole, sulfinpyrazone, dextran
- Drugs which decrease fibrin formation (anticoagulants) - heparin, oral anticoagulants: coumarin (warfarin, bishydroxycoumarin) and indanedione (phenindione) derivatives.
- thrombolytic drugs: streptokinase, urokinase, tissue plasminogen activator
- Miscellaneous drugs which are used to affect hemostasis: aminocaproic acid; tranexamic acid; desmopressin; dihydroergotamine mesylate; pentoxifyllin.

5.3.1.6. 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 2, day -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 Subject Compliance

Study drug will be administered under the supervision of the site personnel.

5.5. Total Blood Volume

The total blood volume to be collected for each subject in this study is approximately 436.9 mL for Part 0 (Table 2, see table footnote), 467.8 mL for Part A (Table 2), 499.6 mL for Part A (0.5 and 1 mg only [Table 3]), and approximately 135.8 mL for Part B (Table 4), where arterial sampling will not be performed.

Table 2: Blood Volumes (Part 0 and Part A)

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Serum chemistry	4.7	4	18.8
Hematology	2.7	4	10.8
Coagulation	2.7	1	2.7
Virology	4.7	1	4.7
Corticoid	4.7	2	9.4
Arterial (1)	2	86	172
Arterial (2)	10	16	160
Pharmacokinetic[a]	2	16	32
Pharmacogenetic	4.9	1	4.9
Biomarkers	10.5	5	52.5
Total			**467.8**

[a] Not applicable for Part 0, where total blood volume will be approximately 436.9 mL.

Table 3: Blood Volumes (Part A [Dose Cohorts 0.5 and 1 mg Only])

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Serum chemistry	4.7	4	18.8
Hematology	2.7	4	10.8
Coagulation	2.7	1	2.7
Virology	4.7	1	4.7
Corticoid	4.7	2	9.4
Arterial (1)	2	86	172
Arterial (2)	10	16	160
Pharmacokinetic	6	16	96
Pharmacogenetic	2.7	1	2.7
Biomarkers	4.5	5	22.5
Total			**499.6**

Table 4: Blood Volumes (Part B)

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Serum chemistry	4.7	4	18.8
Hematology	2.7	4	10.8
Coagulation	2.7	1	2.7
Virology	4.7	1	4.7
Corticoid	4.7	2	9.4
Pharmacokinetic	2	16	32
Pharmacogenetic	4.9	1	4.9
Biomarkers	10.5	5	52.5
Total			**135.8**

6. ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

6.1. Pharmacokinetic Assessment

The following pharmacokinetic parameters will be calculated for pridopidine and its metabolite TV-45065 in plasma using non-compartmental methods, when possible:

C_{max} : maximum observed concentration

t_{max} : time to reach maximum (peak) concentration

AUC_{0-24} : area under the concentration × time curve from time 0 to 24 hours

AUC_{0-t} : area under the concentration × time curve from time 0 to time of last measurable concentration

$AUC_{0-\infty}$: area under the concentration × time curve from time 0 to infinity

$t_{½}$: terminal elimination half-life

V_d/F : apparent volume of distribution of the drug following extravascular administration

Actual sampling times will be used in the analysis.

Additional pharmacokinetic parameters, including partial AUCs and respective average plasma concentration ($C_{average}$) to be inclusive of the PET scan duration, may be calculated as well, as deemed necessary.

6.1.1. Specimen Sampling and Handling

Blood samples (either 6 mL for doses 0.5 and 1 mg [Part A only] or 2 mL for doses ≥2.5 mg) will be collected for analysis of pridopidine and the metabolite TV-45065 up to 1 hour prior to pridopidine dosing, at 5 (±1 minute), 15, 30, 45 and 60 minutes after dosing (±2 minutes), and at 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours after dosing. A 10-minute window will be allowed for all postdose sampling intervals from 1.5 hours up to and including 24 hours after dosing.

Every effort must be made to obtain the pharmacokinetic samples at the scheduled times or within the allowed limits for sampling times, as defined in Table 1. The date and time of each pharmacokinetic sample and the date and time of the last drug administration prior to any collected pharmacokinetic sample will be recorded as source documentation and transcribed onto the CRF. Deviations from the scheduled blood sampling time points will be commented on the respective page of the CRF.

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

Samples will be collected in tripotassium ethylenediaminetetraacetic acid (K_3EDTA)-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 (Nunc cryovials 1.8 mL) (first aliquot [Set A] and back-up [Set B]) and stored below -20°C until bioanalysis.

Sample labels should include the study number, pridopidine dose tracer, permanent unique treatment number, nominal collection time, set (A or B), and indication that they are pridopidine plasma pharmacokinetic samples.

6.1.2. Shipment and Analysis of Samples

Plasma pridopidine and TV-45065 pharmacokinetic samples for all subjects will be shipped from the investigational center to the sponsor or its designee for analysis. Samples will be stored in an upright position at –20ºC or below 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.

Shipments will be made following each cohort, with all samples from individual subject shipped together

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 be sent to the same laboratory as that for Set A on a subsequent day by next-day courier. Set B samples will be sent shortly after arrival of Set A samples.

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.

Samples of cohorts ≥ 2.5 mg of pridopidine will be analyzed using an appropriate validated method for pridopidine and its main metabolite TV-45065 (IRD-MA-119). The lower limits of quantification (LLOQ) for pridopidine and TV-45065 in plasma are approximately 2 ng/mL and 1 ng/mL, respectively. Incurred sample reanalysis may be performed. For cohorts 0.5 and 1 mg pridopidine (Part A only), a lower bioanalytical range will be validated for both pridopidine and TV-45065, with a LLOQ of 40 pg/mL (method IRD-MA-155). Incurred sample reanalysis will be performed.

6.2. Pharmacodynamic Assessment

The imaging procedures will be performed as detailed in the study imaging manual.

6.2.1. Determination of [^{18}F]fluspidine and [^{18}F]Fallypride Functions

During the study period, the subjects will undergo a baseline PET investigation (PET session 1) and a post-dosing PET investigation (PET session 2) following a single oral dose of pridopidine. The PET sessions will be started approximately 2 hours postdose of pridopidine in order to acquire PET images centered around the mean plasma concentration which would be expected on average for repeated dosing every 12 hours. Subjects will have fasted at least 2 hours prior to dosing. Starting with a high dose of 90 mg in dose cohort 1, the subsequent doses for following dose cohort will be determined based on the receptor occupancy determined for previous dose cohorts.

At the day of each PET session, prior to PET imaging, a cubital or forearm vein will be cannulated to inject the PET tracer and, at visit 3, to obtain venous blood samples for

quantification of pridopidine and its metabolite TV-45065 and other exploratory biomarker analysis.

6.2.1.1. [^{18}F]fluspidine (Part 0 and Part A)

The subject's radial artery on the other arm (or the same arm if this cannot be achieved) will be cannulated to obtain arterial blood samples during PET imaging for the quantification of plasma radioactivity associated with the PET tracer in order to estimate a metabolite-corrected arterial plasma input function for PET data analysis. [^{18}F]fluspidine binds to S1R. The PET imaging will consist of 4 blocks with breaks in between: the first PET acquisition block of 90 minutes duration (0 to 90 minutes) will be started together with the intravenous injection of 300±30 MBq [^{18}F]fluspidine as a single bolus, the second acquisition block of 30 minutes duration will be started approximately 2 hours post-injection of the PET tracer (120 to 150 minutes), the third block of 30 minutes duration will be started 3 hours post-injection (180 to 210 minutes), and the fourth block of 30 minutes duration will be started 6 hours (360 to 390 minutes) post-injection. From the second block onwards, acquisition can commence within ±10 minutes of the nominal time, but the duration should still be 30 minutes for each of these blocks. Each PET acquisition block will be acquired in list mode in order to allow variable subdivision into multiple time frames. The PET session 2 will start 2 hours postdose of pridopidine. Prior to any blocking with pridopidine, a test-retest will be performed for up to 6 subjects under similar conditions. In an effort to facilitate easier PET procedure for HD patients, after the first 90-minute PET acquisition block, the subsequent 30-minute PET acquisition blocks are made optional per Investigator's judgement.

Test-retest variability of [^{18}F]fluspidine uptake will be estimated using 2 baseline [^{18}F]fluspidine scans in up to 6 subjects. This will be used to calculate the uncertainty of the RO estimate.

Appropriate analysis will be performed to estimate the S1R binding potential and RO. Available evidence suggests that there is no viable reference region in the brain for [^{18}F]fluspidine that can be used for modeling purpose. Therefore, metabolite-corrected arterial plasma input function will be estimated and used in the calculation of regional PET volume of distribution (V_T), regional binding potential (BP_{ND}) and RO defined as the treatment-induced relative change in the concentration in the available receptor density as:

$$RO = \left(1 - \frac{BP_{ND}(treatment)}{BP_{ND}(baseline)}\right) \times 100\%$$

Where BP_{ND}(treatment) is the binding potential under the treatment condition and BP_{ND}(baseline) the binding potential at baseline. The BP_{ND} is a parameter proportional to the density of the available receptors and the affinity of the tracer to the receptor.

Due to the fact that a reference region most likely does not exist the following procedure is likely be used to derive the relevant PET parameters:

- V_T, representing the total radioligand in tissue (ie, free, non-displaceable and specifically bound) and a global non-displaceable volume of distribution (V_{ND}) will be calculated for each brain region and for each postdose scan using appropriate compartmental models.
- V_T and V_{ND} will allow the estimation of BP_{ND}, and the global occupancy.

RO expressed as a percentage will be calculated for each subject and each postdose scan.

Spatial normalization of the PET scan to a brain atlas template will be performed using a corresponding MRI scan. All PET parameters will be calculated globally, for the whole brain, and for specific predefined brain areas.

6.2.1.2. [^{18}F]fallypride (Part B)

[^{18}F]fallypride binds to D2R in striatal and to a lesser extent in extra-striatal regions. The PET imaging will consist of 4 blocks with breaks in between: the first PET acquisition block of 90 minutes duration (0 to 90 minutes) will be started together with the intravenous injection of 200±20 MBq [^{18}F]fallypride as a single bolus, the second acquisition block of 30 minutes duration will be started approximately 2 hours post-injection of the PET tracer (120 to 150 minutes), the third block of 30 minutes duration will be started 3 hours post-injection (180 to 210 minutes), and the fourth block of 30 minutes duration will be started 6 hours (360 to 390 minutes) post-injection. From the second block onwards, acquisition can commence within ±10 minutes of the nominal time, but the duration should still be 30 minutes for each of these blocks. Each PET acquisition block will be acquired in list mode in order to allow variable subdivision into multiple time frames. The PET session 2 will start approximately 2 hours postdose of pridopidine. In an effort to facilitate easier PET procedure for HD patients, after the first 90-minute PET acquisition block, the subsequent 30-minute PET acquisition blocks are made optional per Investigator's judgement.

The cerebellum can be used as a reference region for [^{18}F]fallypride since it has been shown to have a minimal presence or a lack of D2 receptors, and therefore the simplified reference tissue model can be applied.

Reference region: cerebellum (excluding vermis) using Automated Anatomical Labeling atlas.

Specific binding regions of interest: caudate, putamen, medial inferior temporal gyri, thalamus, amygdala, hippocampus, arbitofrontal cortex, anterior cingulate gyrus using Tzioritzi atlas plus striatum with subdivisions in [redacted] using anterior/posterior commissure transaxial plane.

7. ASSESSMENT OF SAFETY

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

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

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

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

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

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

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the subject from the study, are associated with clinical signs and symptoms or a serious adverse event, 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 subject from entering the study or receiving study treatment are not considered adverse events.)

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse event, the study period is defined for each subject as that time period from signature of the informed consent form to the end of the follow-up period. The follow-up period is defined as 7 days after the last dose of study drug.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed to the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the serious adverse event form must be completed and the serious adverse event must be reported immediately (see Section 7.1.5.3.1). The investigator does not need to actively monitor subjects for adverse events once the study has ended. Serious adverse events occurring in a subject after the treatment of that subject 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 subject, the investigator or designee must question the subject about adverse events by asking an open-ended question such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe”. All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the subject is referred for continued care to 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 and times, duration, action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed to the CRF.

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

7.1.3. Severity of an Adverse Event

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

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Study Drug

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

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

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

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

- death
- a life-threatening adverse event (ie, the subject was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

Hospitalizations scheduled before the subject signed the informed consent form will not be considered serious adverse events, unless there was worsening of the preexisting condition during the subject's participation in this study.

- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed in this definition

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **al**l of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of >3× the upper limit of normal (ULN)
- total bilirubin elevation of >2× ULN
- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase)

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

7.1.5.2. Expectedness

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

The sponsor's Global Patient Safety and Pharmacovigilance will determine the expectedness for all serious adverse events.

For the purpose of suspected unexpected serious adverse reaction (SUSAR) reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during the study period (including the protocol-defined follow-up period, described in Section 7.1.2), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when

the investigator learns about it. Completing the serious adverse event 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 subjects for adverse events once this study has ended.

Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the sponsor's LSO in Germany (contact information is in the Clinical Study Personnel Contact Information section).

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

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

Additional information may include the following:

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

The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Each report of a serious adverse event 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 serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

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

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

7.1.5.3.2. Sponsor Responsibility

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

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

- 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 all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to pridopidine

7.1.6. Protocol-Defined Adverse Events for Expedited Reporting

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

7.1.7. Withdrawal Due to an Adverse Event

Any subject who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator. If a subject is withdrawn wholly or in

part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time.

In addition, a blood sample will be obtained for the measurement of study drug concentrations. The subject will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the subject 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 clinical project physician (CPP)/clinical leader (CL) as soon as possible of each subject who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a subject is withdrawn from the study drug for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the subject. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

7.1.8. Overdose of Study Drug

Any dose of study drug (whether the investigational product or tracers), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.

7.1.9. Protocol Deviations Because of an Adverse Event

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

7.2. Pregnancy

Only male healthy subjects and (optional) HD patients will be enrolled in this study.

All pregnancies of female partners of men participating in the study that occur within 3 months of completion of the study, are to be reported immediately to the physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the LSO/CRO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (see Section 7.1.5.3).

7.3. Medication Error and Special Situations

Any administration of medication that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria specified in the protocol (Section 11.1.2), or as a deviation, in the subjects source documents, regardless of

whether an adverse event occurs as a result. All instances of incorrect medication administration should be categorized on the CRF as "Non-Compliance to investigational medicinal product (IMP)".

Types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, subject, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
3. Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to a medicinal product, as a result of one's professional or non-professional occupation.

7.4. Clinical Laboratory Tests

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

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded on the source documentation, transcribed to the CRF as an adverse event, and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the subject from the study, the temporary or permanent cessation of treatment with study drug or medical treatment, or further diagnostic work-up.

In addition, potentially clinically significant values may be predefined by the sponsor for selected laboratory test variables (see Section 9.10.2) and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan or laboratory analysis plan).

7.4.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. Clinical laboratory tests will be performed using a central laboratory. Specific laboratory tests to be performed are provided in Table 5.

Table 5: Clinical Laboratory Tests

Serum Chemistry	Hematology and Coagulation	Urinalysis
calcium phosphorus sodium potassium magnesium chloride glucose blood urea nitrogen (BUN) creatinine (including calculation of creatinine clearance using the Cockcroft-Gault formula) cholesterol (low density lipoprotein (LDL)/high density lipoprotein (HDL) /total) uric acid alanine aminotransferase (ALT) aspartate aminotransferase (AST) lactate dehydrogenase (LDH) gamma-glutamyl transpeptidase (GGT) alkaline phosphatase creatine phosphokinase (CPK) - in case of elevated CPK, the MB fraction should be measured total protein albumin total bilirubin direct bilirubin indirect bilirubin prolactin	hemoglobin hematocrit red blood cell (RBC) count RBC indices platelet count white blood cell (WBC) count, and differential count and percentage – absolute neutrophil count (ANC) – polymorphonuclear leukocytes (neutrophils) – lymphocytes – eosinophils – monocytes – basophils – atypical lymphocytes Prothrombin International Normalized Ratio (INR) Activated partial Thromboplastin Time (aPTT)	protein glucose ketones blood (hemoglobin) pH specific gravity microscopic – bacteria – RBCs – WBCs – casts – crystals

7.4.2. Other Clinical Laboratory Tests

At screening, subjects will be tested for HIV-1, HIV-2, HBsAg, and hepatitis C antibody.

7.4.2.1. Urine Drug Screen

A urine drug screen will be performed at screening and on day -1. The drug screen will detect the presence of amphetamines, cocaine, opiates, cannabis, barbiturates, and benzodiazepine. A positive result for any of these drugs or their metabolites, without medical explanation, will preclude the subject from enrollment or continued participation in the study.

7.4.2.2. Corticoid Plasma Levels

Endogenous corticoid plasma levels will be measured on day 1 of visits 2 and 3 (immediately before the tracer injection). The analysis will include measurement of DHEA, progesterone, testosterone, cortisol, and, where feasible, androstanolone, allopregnanolone, pregnenolone.

7.5. Vital Signs

Vital signs (pulse, BP, body temperature, and respiratory rate) will be measured at the time points detailed in Table 1. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

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

In addition, potentially clinically significant values may be predefined by the sponsor for selected vital signs (see Section 9.10.2) and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan).

When vital signs collection coincides with a pharmacokinetic sample, vital signs will be collected before the pharmacokinetic sample.

7.6. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 1. A qualified physician will be responsible for interpreting the ECG. Any ECG finding that is judged by the investigator as clinically significant will be considered an adverse event, recorded on the source documentation, transcribed to the CRF, and monitored as described in Section 7.1.2.

The 12-lead ECG is to be performed before pridopidine administration; immediately before administration of the tracer (approximately 90 minutes after pridopidine administration), and at the end of the first PET scan (approximately 3.5 hours after pridopidine administration).

When ECG collection coincides with a pharmacokinetic sample, ECG will be collected before the pharmacokinetic sample.

7.7. Physical Examinations

Physical examinations, including height and weight (to be obtained at the screening visit only), will be performed at the time points detailed in Table 1. Any new physical examination finding that is judged by the investigator as clinically significant will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

A complete physical examination will be performed at screening and at the follow-up/ET visits only. On other occasions, an abbreviated/symptom-oriented physical examination will be performed.

7.8. Concomitant Medication or Treatment

Use of concomitant medication or treatment will be monitored throughout the study. Details of prohibited medications are found in Section 5.3.

7.9. Assessment of Local Tolerability and Pain

Local tolerability at the injection site of the tracer (eg, pain, erythema, ecchymosis, induration) will be evaluated as part of the standard medical supervision during administration.

7.10. Modified Allen Test

The Modified Allen Test will be performed at screening for Part 0 and Part A subjects only.

A modified Allen test measures arterial competency, and should be performed for both hands. The procedure for performing the test is as follows (derived from [redacted]

1. The subject is instructed to clench his fist; if the subject is unable to do this, the subject's hand is to be tightly closed by the assessor.
2. Using fingers, occlusive pressure is applied to both the ulnar and radial arteries, to obstruct blood flow to the hand.
3. While applying occlusive pressure to both arteries, the subject should relax his hand, and a check is performed as to whether the palm and fingers have blanched, to ensure that the arteries are completely occluded.
4. The occlusive pressure on the ulnar artery is released to determine whether the modified Allen test is positive or negative:
   - Positive modified Allen test – If the hand flushes within 5 to 15 seconds it indicates that the ulnar artery has good blood flow; this normal flushing of the hand is considered to be a positive test.
   - Negative modified Allen test – If the hand does not flush within 5 to 15 seconds, it indicates that ulnar circulation is inadequate or nonexistent.

7.11. Columbia Suicide Severity Rating Scale

The C-SSRS (screening version) will be used at screening to rate the subject'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). Subjects with a history of suicidality based upon clinical history or C-SSRS scoring will not be eligible for the study. The person administering the C-SSRS should have performed the rater training and have obtained a training certificate within the previous 2 years.

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

The version of C-SSRS used will be translated into German and linguistically validated.

7.12. Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) (HD Patients Only)

For HD patients only, UHDRS-TMS is performed at the time points detailed in Table 1.

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

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).

7.13. Methods and Time Points of Assessing, Recording, and Analyzing Safety Data

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

Methods and time points of assessing safety data are discussed in Section 3.14. Procedures for recording safety data are discussed in Section 13.1 and methods of analyses are discussed in Section 9.10.2.

8. ASSESSMENT OF BIOMARKERS AND PHARMACOGENETICS

8.1. Assessment of Exploratory Biomarkers

8.1.1. Biomarker Assessments

Biomarkers are defined as biological substances that monitor physiological effects, assessing drug activity, predicting clinical outcome, safety, and treatment response.

Biomarker assessment potentially includes the following:

[redacted]

The final list of biomarkers that will be investigated will be selected at a later stage before the analysis so as to allow updating with new scientific information.

8.1.2. Pharmacogenetic Assessment

[redacted] and it is known that subjects with functional mutations resulting in inactive enzyme will show higher exposures and are at greater risk of known emergent adverse events. As a result, DNA will be collected, and subjects identified as poor CYP2D6 metabolizers will be excluded from the study. Remnant DNA will also be genotyped to identify extensive, intermediate and ultra CYP2D6 metabolizers. Genotyping may also be conducted for QTc in the event of any emergent safety findings. In addition, functional genetic polymorphisms have been described in the S1R receptor that results in decreased receptor expression (Miyatake et al 2004). Examination of the known S1R polymorphisms did not impact fluvoxamine displacement with SA4503 (Ishikawa et al 2007). However, the impact of these polymorphisms on fluspidine displacement is not known. [redacted]

[redacted]

Genetic long QT syndrome genotyping may also be conducted retrospectively and assessed only in subjects experiencing QT prolongation following study drug administration leading to study discontinuation. Blood sampling for pharmacogenetics can be performed at a separate visit within the screening period after informed consent is obtained.

8.1.3. Specimen Sampling and Handling

8.1.3.1. Biomarker Samples

For all dose cohorts ≥2.5 mg, biomarker blood samples of 4 mL to provide 2 mL serum, 4 mL to provide 2 mL plasma, with an additional 2.5 mL collected in a PAXgene tube will be collected. For the 0.5 and 1 mg dose cohort in Part A, biomarker blood samples of 2 mL for plasma, 2.5 mL of PAXgene tube, and no serum samples will be collected.

The date and time of each biomarker sample and the dates and times of the last drug administration prior to any collected biomarker 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 the biomarker blood sample collection coincides with pharmacokinetic measures, the biomarker samples should be collected after pharmacokinetic sampling.

For plasma, samples will be collected in lavender-top (K_3EDTA) Vacutainer venous blood collection tubes following site standard phlebotomy practices and procedures. Immediately following collection, the tube should be gently inverted 4 to 8 times, and cooled on wet ice. Within 45 minutes of collection, the tube should be centrifuged at approximately 4°C at 1500 × g for 15 minutes. The plasma should then be immediately transferred into 2 polypropylene tubes (first aliquot [Set A] and back-up [Set B]) and stored below -70°C (or -20°C in a non-defrosting freezer if -70°C is not available) until shipment to the sponsor specified biorepository [redacted]), where they will be retained for at least 15 years.

For serum, samples will be collected into red-top Vacutainer tubes (serum separators should not be used) following site standard phlebotomy practices and procedures. Tubes should be gently inverted 4 to 6 times and stored upright at room temperature for 30 to 45 minutes. Within 45 minutes of collection, tubes should be centrifuged at approximately 4°C at 1500 × g for 15 minutes. The serum should then be immediately transferred into 2 polypropylene tubes (first aliquot [Set A] and back-up [Set B]) and stored below -70°C (or -20°C in a non-defrosting freezer if -70°C is not available) until shipment to the sponsor specified biorepository [redacted]), where they will be retained for at least 15 years.

For RNA, samples will be collected into a PAXgene blood RNA tube at room temperature following site standard phlebotomy practices and procedures. The PAXgene tube should be collected after the serum and plasma collections and held in an upright vertical position below the donor's arm during blood collection. For a complete blood draw, at least 10 seconds should be allowed and it should be ensured that blood has stopped flowing into the tube before

removing from the holder. The PAXgene blood RNA tube should be gently inverted (not shaken) 8 to 10 times and stored upright at room temperature. The tube should be incubated at room temperature for 2 hours to ensure complete lysis before freezing. Samples should be frozen for at least 24 hours at -20°C and then transferred to -70°C until shipment to the sponsor specified biorepository [redacted]), where they will be retained for at least 15 years.

8.1.3.2. Pharmacogenetic Samples

Pharmacogenetic blood samples will be collected at screening only. For all dose cohorts ≥2.5 mg, the pharmacogenetic blood should be collected into a 4.9-mL (K_3EDTA) Sarstedt Monovette® venous blood collection tube labeled with the subject coded number and following site standard phlebotomy practices and procedures. For the 0.5 and 1 mg dose cohort in Part A, the pharmacogenetic blood should be collected into a 2.7-mL (K_3EDTA) Sarstedt Monovette® venous blood collection tube labeled with the subject coded number and following site standard phlebotomy practices and procedures.

Immediately following collection, the tube should be gently inverted (not shaken) 4 to 8 times. The tubes must not be centrifuged. Samples are to be stored and shipped at 4°C if they are to arrive to the genotyping laboratory within 48 hours for CYP2D6 genotyping; if not, samples should be stored at -20°C in a non-defrosting freezer at the study site until shipment [redacted]

8.1.4. Shipment and Analysis of Samples

8.1.4.1. Biomarker Samples

Biomarker sample aliquots should be shipped on dry ice by overnight courier to [redacted] and stored at -70°C. Vendor contact details will be provided by the sponsor.

8.1.4.2. Pharmacogenetic Samples

Pharmacogenetic samples should be shipped by overnight courier to a specified vendor [redacted] during screening (either ambient if to be received by the genotyping laboratory within 48 hours or on dry ice if stored at -20°C). Remnant DNA should be retained and stored at the vendor until the end of study and then shipped to the biorepository [redacted] The remnant samples will be labeled with a new code so genetic data will not be recorded with a subject number.

9. STATISTICS

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

9.1. Sample Size and Power Considerations

This PET study is exploratory in nature; therefore, no formal hypothesis testing is planned. Thus, based on clinical and practical considerations, a sample size of up to approximately 38 subjects (up to 4 subjects per dose level) is considered adequate for this type of study and to attain the study objectives. Up to 45 subjects are planned to be enrolled in this study to ensure up to 38 evaluable subjects. Adaptive study design will allow increasing or reducing the study total sample size or each dose/time cohort as necessary. This sample size may include up to 4 patients with HD, which may be added to study engagement of pridopidine to the D2R and to explore the effects of neurodegeneration.

It is anticipated that 3 dose levels will be sufficient to characterize the exposure-response profile. However, additional cohorts may be studied.

9.2. Analysis Sets

9.2.1. Enrolled Analysis Set

The enrolled analysis set will include all enrolled subjects, regardless of whether or not a subject took any study drug. A subject is considered enrolled according to the status reported in the database.

9.2.2. Safety Analysis Set

The safety analysis set will include all subjects who receive at least 1 dose of study drug. In this analysis set, treatment will be assigned based on the treatment subjects actually received.

9.2.3. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include those subjects in the safety analysis set who have sufficient data to calculate at least 1 evaluable pharmacokinetic parameter for pridopidine or its metabolites.

9.2.4. Pharmacodynamic Analysis Set

The pharmacodynamic analysis set will include those subjects in the safety analysis set who have evaluable imaging data before and after pridopidine administration.

9.3. Data Handling Conventions

For all variables, only the observed data from the subjects will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified. Detailed data imputation rules will be described in statistical analysis plan.

9.3.1. Handling Withdrawals and Missing Data

Missing data will not be imputed, unless otherwise specified.

9.4. Study Population

The enrolled analysis set (see Section 9.2) will be used for all study population summaries unless otherwise specified.

9.4.1. Subject Disposition

Data from subjects screened, subjects screened but not enrolled (and reason not enrolled), subjects who are enrolled, subjects enrolled but not treated (and reason), subjects in the safety and pharmacokinetic analysis sets, subjects who complete the study, and subjects who withdraw from the study will be summarized using descriptive statistics. Data from subjects who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.4.2. Demographic and Baseline Characteristics

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

9.5. Pharmacodynamic Analysis

9.5.1. Analysis with (S)-(-)-[^{18}F]fluspidine

Details of the analysis to be performed are presented in Section 6.2.1.1.

The occupancy data for the study will be combined with the plasma concentration of pridopidine and used to derive the in vivo affinity of pridopidine for the S1R and the time-course of the occupancy of S1R by pridopidine.

Test-retest variability of (S)-(-)-[^{18}F]fluspidine uptake will be estimated using 2 baseline (S)-(-)-[^{18}F]fluspidine scans in up to 6 subjects. This will be used to calculate the uncertainty of the RO estimate.

9.5.2. Analysis Using [^{18}F]fallypride

The analysis using [^{18}F]fallypride will be similar to that using (S)-(-)-[^{18}F]fluspidine.

For calculation of BP_{ND} and RO for [^{18}F]fallypride, a tissue reference model can be used using the cerebellum as reference region without specific binding.

9.6. Pharmacokinetic Analysis

The pharmacokinetic parameters to be calculated for pridopidine and its metabolite TV-45065 in the plasma using non-compartmental methods, when possible, are detailed in Section 6.1.

Additional pharmacokinetic parameters, including partial AUCs and corresponding $C_{average}$ to be inclusive of the PET scan duration, may be calculated as well, as deemed necessary.

No formal statistical analyses of the pharmacokinetic data will be performed. All data will be listed and summarized descriptively by cohort (dose) and status (healthy subject or HD patient) and presented in tabular and graphical form where appropriate. The pharmacokinetic analysis set (see Section 9.2.3) will be used for all pharmacokinetic analyses.

9.7. Pharmacokinetic/Pharmacodynamic Analysis

The relationship between the pridopidine plasma concentrations and the RO will be explored graphically. If possible, an exposure-response model will be developed to quantitatively define the relationship between RO and pridopidine exposure. It will be based on the following E_{max} model (equation) to fit the pharmacokinetic-pharmacodynamic (PK/PD) data (Grachev et al 2014):

$$E = \frac{E_{max} \times C}{EC_{50} + C}$$

Where E represents the receptor occupancy (%); C is the plasma concentration (ng/mL) corresponding to the receptor occupancy E; E_{max} is an asymptote representing the maximum receptor occupancy (%); EC_{50} is the plasma concentration (ng/mL) corresponding to 50% of E_{max}.

Two additional parameters derived to characterize various levels of receptor occupancy are:

- EC_{80} - the plasma concentration (ng/mL) corresponding to 80% of E_{max}. It is calculated directly from the equation by substituting E=80% of E_{max} and then solving for C.
- EC_{opt} - plasma concentration (ng/mL) corresponding to optimal receptor occupancy. EC_{opt} was defined as the lowest observed plasma concentration that achieved the model estimated E_{max}.

Details of the analysis will be provided in a separate analysis plan.

9.8. Planned Method of Analysis

The enrolled analysis set (see Section 9.2.1) will be used for all pharmacodynamic analyses. Summaries will be presented by treatment group.

9.9. Multiple Comparisons and Multiplicity

No adjustments will be made for the preplanned multiple comparisons/endpoints.

9.10. Safety Endpoints and Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.2).

9.10.1. Safety Endpoints

Safety measures and time points are provided in Table 1.

9.10.2. Safety Analysis

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

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with predefined criteria to identify potentially clinically significant values or changes, 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 subject is treated with study drug.

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

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

9.11. Tolerability Variables and Analysis

Subject tolerability assessments (the number [%] of subjects who fail to complete the study, number [%] of subjects who fail to complete the study due to adverse events, and the number of subjects who experience treatment-emergent adverse events) will be summarized.

9.12. Pharmacogenetic and Biomarker Analysis

Levels in exploratory biomarkers will be compared to baseline and summary tables may be generated. Exploratory biomarker results will be generated at a future point and handled in a separate addendum report.

9.13. Relationship Between Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) and Other Endpoints

Relationships between UHDRS-TMS (absolute score and change from baseline) and other endpoints will be evaluated in HD patients. Details of this analysis will be presented in the statistical analysis plan.

9.14. Planned Interim Analysis

There will be no formal interim analysis.

9.15. Reporting Deviations from the Statistical Plan

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

10. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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

The investigator must maintain the original records (ie, source documents) of each subject'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 3.13).

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

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments and Protocol Deviations and Violations

11.1.1. Protocol Amendments

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

11.1.2. Protocol Violations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the subjects of the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol violations may include non-adherence on the part of the subject, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; use of prohibited medications. Protocol violations will be identified and recorded by investigational center personnel in 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 subject from the study or permit the subject to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the subject and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a subject who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol violation. If such subject 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

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of subject management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel 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 personnel, including the investigator, and for ensuring they comply with the protocol. Additional information will be

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

The study monitor will contact the investigator and visit the investigational center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, including specific electronic source document [see Section 3.13]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic CRFs are used for the study, the study monitor will indicate verification by electronically applying source document verification flags to the CRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel 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 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 or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both

- device not working correctly or appears defective in some manner

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

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the subject'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 PI name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- subject identifier (subject study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- subject 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 product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

11.4.2. Handling of 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 study drug, the sponsor will provide the information needed to handle the return.

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

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

11.4.4. Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the subject. 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, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Clinical Development, is responsible for determining the need for (and timing of) an investigational center audit.

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

12. ETHICS

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

12.1. Informed Consent

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

Written informed consent will be obtained from each subject 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 subject's willingness to participate in the study will be documented in the informed consent form, which will be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The investigator will keep the original informed consent forms, and copies will be given to the subjects. It will also be explained to the subjects that the subject is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Adult subjects with a legally acceptable representative should provide informed consent according to national and local requirements.

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

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

12.3. Confidentiality Regarding Study Subjects

The investigator must ensure that the privacy of the subjects, 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, subjects will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of subject safety or for verifying data in the source and transcribed to the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance, or competent authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of Clinical Study

For 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, national and local regulations will be followed.

12.5. Registration of the Clinical Study

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

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

13.1. Data Collection

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

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

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

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

13.2. Data Quality Control

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

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. The system requires a reason for each change and keeps a complete audit trail of the data values, dates, and times of modifications, and authorized electronic approvals of the changes.

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

13.3. Archiving of Case Report Forms and Source Documents

13.3.1. Sponsor Responsibilities

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

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

13.3.2. Investigator Responsibilities

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

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

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements

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

14. FINANCING AND INSURANCE

[redacted]

15. REPORTING AND PUBLICATION OF RESULTS

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

The sponsor is responsible for the preparation of a CSR, in cooperation with the PI. The final report is signed by the sponsor and, if applicable, by the PI.

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

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

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

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

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

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