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

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Statistical Analysis Plan

Study 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

Approval Date: 01 February 2018

Sponsor

Teva Branded Pharmaceutical Products R&D, Inc.

[redacted]

Prepared by: [redacted]
Senior Biostatistician, PRA Health Sciences – Early Development Services

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **TV7820-IMG-10082**

Study Title: **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**

Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

Author: [redacted]

Senior Biostatistician, PRA Health Sciences – Early Development Services

[redacted] 1FEB2018

Approver: **Date**

Statistical Head of Clinical Pharmacology

Approver: [redacted] **Date**

Sr Dir, Global Clin Dev Leader & Clinical Project Physician Movement Disorders

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **TV7820-IMG-10082**

Study Title: **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**

Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

Author: **Mieke Kruizinga, BSc**

Senior Biostatistician, PRA Health Sciences – Early Development Services

Approver: [redacted] **Date**

Statistical Head of Clinical Pharmacology

Approver: [redacted] 1/31/2018 **Date**

Sr Dir, Global Clin Dev Leader & Clinical Project Physician Movement Disorders

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ASL	arterial spin labeling
BP	blood pressure
BQL	below the quantification limit
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
CYP2D6	cytochrome P450 2D6
D2R	dopamine-2 receptor
DHEA	dehydroepiandrosterone
ECG	electrocardiogram
HD	Huntington's disease
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MR-AC	MRI-based Attenuation Correction
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
PET	positron emission tomography
R&D	Research and Development
RO	receptor binding/occupancy
Rs-fMRI	resting state functional magnetic resonance imaging
S1R	sigma-1 receptor
SAP	statistical analysis plan
SD	standard deviation
SI	standard international
SOC	system organ class
SOP	standard operating procedure
T1 MPRAGE 3D	T1-weighted rapid 3-dimensional gradient-echo technique
ULN	upper limit of normal

Abbreviation	Term
WHODD	World Health Organization drug dictionary
WNL	WinNonlin®

A detailed description of the pharmacokinetic parameters can be found in Section 9.2.

INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. study 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).

The following documents are used or referred to for the SAP generation:

- Clinical study protocol with Amendment 01, Approval date 11 November 2016
- Case report forms (CRFs) for Study TV7820-IMG-10082
- International Council for Harmonisation (ICH) E9 Guidance on Statistical Principles for Clinical Trials
- ICH E3 Structure and Content of clinical study reports

The reader of this SAP is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a subject in this study.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (eg, other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this SAP, the SAP prevails; the differences will be explained in the clinical study report (CSR).

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Study Objectives and Endpoints

1.1.1. Primary and Secondary Study Objectives

The primary objective 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.

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.

1.1.2. Endpoints

1.1.2.1. Pharmacodynamic Endpoints

The PET acquisition, as well as advanced magnetic resonance imaging (MRI) protocols (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]) will be detailed in dedicated imaging manuals. These will also contain an analysis plan explaining how the imaging data is calculated. Imaging manuals will be provided prior to initiating the study.

1.1.2.2. 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 9.2.

1.1.2.3. 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
- 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

1.1.2.4. Biomarker Endpoints

[redacted]

1.1.2.5. Pharmacogenetic Endpoints

[redacted]

1.2. Exploratory Objectives and Endpoints

1.2.1. 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;
- 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]

1.2.2. Exploratory Endpoints

Exploratory endpoints will be defined in the imaging analysis plan.

2. STUDY DESIGN

2.1. General Design

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).

Since endogenous corticoid hormones have been described to competitively bind to S1R, the test-retest variability of (S)-(-)-[18F]fluspidine PET will be determined in 3 healthy subjects up-front or 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 cytochrome P450 2D6 (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 at visits 2 and 3 to inject (S)-(-)-[^{18}F]fluspidine and only on visit 3 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.

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 (2.5, 5, 10, 22.5, 45, or 67.5 mg) 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.

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.

Study procedures and assessments with their time points are summarized in Table 1 of the study protocol.

2.2. Randomization and Blinding

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

2.3. Data Monitoring Committee

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

2.4. 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.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

There will be no formal interim analysis for this study. PET data will be analyzed after each cohort for selection of the next cohort dose.

2.5.2. Final Analyses and Reporting

All final, planned analyses for pharmacokinetic and safety measures identified in this SAP will be performed after the end of study as defined in the study protocol. This SAP and any corresponding amendments will be approved before database lock, in accordance with SOP GBP_RD_702 (SAP).

All analyses for pharmacodynamics (imaging data) will be detailed in the imaging manual prepared by [redacted]

[redacted]

3. ANALYSIS SETS

3.1. 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.

3.2. Safety Analysis Set

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

3.3. 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.

3.4. 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. The decision about inclusion and exclusion of subjects in this analysis set will be done after Teva will receive final PD data.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. For continuous pharmacokinetic parameters (except t_{max}), the geometric mean will also be calculated. Descriptive statistics for categorical variables include subject counts and percentages, missing category will be displayed as appropriate.

For presentation the mean and median will be presented to 1 decimal greater than the original data, SD will be 2 greater than the original data and the minimum and maximum will have the same number of decimal places as the original data. The derived pharmacokinetic parameters will be summarized with a precision of 3 significant digits, while t_{max} will be presented with 2 decimals. The percentage coefficient of variation (CV) and frequency percentages will be presented with 1 decimal.

Tables will be presented by part and cohort, unless otherwise specified. Throughout the document cohort will mean the combination of dose level and population (healthy volunteers or patients with HD).

In case different dose levels are used within a cohort the cohort will be split by dose level. In case similar dose levels are used in different cohorts within the same population, these data may be pooled.

4.2. Specification of Baseline Values

Baseline for postdose evaluations is defined as the last observation recorded before the first study drug administration. The last observation can be an unscheduled / repeated measurement.

4.3. Handling Withdrawals and Missing Data

No imputation of missing data is planned, except for pharmacokinetic plasma concentration below the quantification limit (BQL) (see Section 9.3.1 and Section 9.3.2) and missing dates and times for AEs (see section 7.2).

4.4. Study Days and Visits

For by-visit (or by-time-point) summaries, if there are multiple assessments at a post baseline visit (or time point) then the scheduled assessment at that visit (or time point) will be used for the summary. For baseline and pre-baseline visits the last non-missing assessment at that visit (or time point) will be used for the summary (this includes scheduled and unscheduled assessments). For subjects who withdraw from the study, data at the early termination visit will be excluded from the by-visit summaries but will be included in the endpoint summaries.

An early termination visit is defined as the follow-up visit for a subject that did not complete the study.

Unscheduled measurements will be listed in the individual data listings.

Study days will be numbered relative to the first day of study drug administration in each visit (ie, visit 2 and visit 3). The start of treatment (day 1) is defined as the date on which a subject takes the first dose of study drug, as recorded on the CRF. Days will be numbered relative to treatment start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the first day of study drug administration and day –1 being the day before the first day of study drug administration).

5. STUDY POPULATION

5.1. General

The enrolled analysis set will be used for all study population summaries unless otherwise specified. Summaries will be presented by part and cohort, unless otherwise specified.

5.2. 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. The data will also be presented in a listing.

5.3. Demographics and Baseline Characteristics

Subject demographic and baseline characteristics, including medical history, and prior medications will be summarized using descriptive statistics by part and cohort. The results of the C-SSRS at screening will be listed.

5.4. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term. Subjects are counted only once in each preferred term and SOC category.

5.5. Prior Therapy and Medication

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 therapy, medication, or procedure a subject has had within 28 days before study drug administration will be recorded on the CRF. Trade name or INN, 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 (WHODD).

5.6. Study Protocol Violations

Data from subjects with any protocol violations (as recorded in the protocol violation CRF) during the study will be summarized overall and for each category using subject counts and percentages.

6. MULTIPLE COMPARISONS AND MULTIPLICITY

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

7. SAFETY ANALYSIS

7.1. General

The safety analysis set will be used for all safety analyses. Summaries will be presented by part and cohort, unless otherwise stated.

7.2. Adverse Events

All adverse events will be coded using MedDRA.

Adverse events present before the first administration of study drug (PET tracer) will not be included in the summaries.

The incidence of adverse events will be summarized using descriptive statistics by SOC and preferred term. 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) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. For the summaries by severity, subjects are counted at the highest severity. Summaries will be presented by part, cohort and total by population for all subjects.

All adverse events (including events started before the first administration of study drug) recorded on the CRF will be listed. Subject listings of serious adverse events and adverse events leading to withdrawal will also be presented.

The following missing data will be imputed as defined (for calculations only, will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date
- Missing AE start date will be assumed to be after treatment for deaths and SAEs.

7.3. Deaths

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.

7.4. Clinical Laboratory Tests

Laboratory test results will be presented in standard international (SI) units. All laboratory data will be listed.

Summary statistics for chemistry, hematology, and urinalysis laboratory tests will be presented for screening, visits 2 and 3, and for the follow-up visit. Summary statistics for coagulation laboratory test will be presented for screening. Laboratory tests values and changes from baseline (absolute) to each visit and time point will be summarized using descriptive statistics.

All values will be compared with predefined criteria, as specified in Table 1, to identify potentially clinically significant values or changes. These values will be listed in the subject data listings. The incidence of potentially clinically significant abnormal values will be summarized for laboratory variables using subject counts as specified in Section 4.1.

Table 1: Criteria for Potentially Clinically Significant Laboratory Values

Test	Criterion value
Serum chemistry	
Alanine aminotransferase (ALT)	≥3x ULN
Aspartate aminotransferase (AST)	≥3x ULN
Alkaline phosphatase	≥3x ULN
Gamma-glutamyl transpeptidase (GGT)	≥3x ULN
Lactate dehydrogenase (LDH)	≥3x ULN
Blood urea nitrogen (BUN)	≥10.71 mmol/L
Creatinine	≥177 µmol/L
Uric acid Men	≥625 µmol/L
Bilirubin (total)	≥34.2 µmol/L
Hematology	
Hematocrit Men	<0.37 L/L
Hemoglobin Men	≤115 g/L
White blood cell (WBC) counts	≤3 x 10^9/L, ≥20 x 10^9/L
Eosinophils	≥10%
Absolute neutrophil counts (ANC)	≤1 x 10^9/L
Platelet counts	≤75 x 10^9/L, ≥700 x 10^9/L
Urinalysis	
Blood (HGB)	≥2 unit increase from baseline
Glucose	≥2 unit increase from baseline
Ketones	≥2 unit increase from baseline
Total protein	≥2 unit increase from baseline

ULN=upper limit of normal range

7.4.1. Laboratory Values Meeting Hy's Law Criteria

All occurrences of possible drug-induced liver injury that meet Hy's law criteria as defined in protocol Section 7.1.5.1 will be included in adverse events reporting.

7.4.2. Other Clinical Laboratory Tests

At screening, subjects will be tested for human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B surface antigen, and hepatitis C antibody. These results will be presented in the subject data listings.

7.4.2.1. Urine Drug Screen

A urine drug screen will be performed at screening and on visits 2 and 3. The drug screen will detect the presence of amphetamines, cocaine, opiates, cannabis, barbiturates, and benzodiazepine. The urine drug screen results will be presented in the subject data listings.

7.4.2.2. Alcohol Screen

An alcohol breath analyzer test will be performed at screening and on visits 2 and 3. These results will be presented in the subject data listings.

7.4.2.3. Corticoid Plasma Levels

Endogenous corticoid plasma levels will be measured on 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. These results will be presented in the subject data listings.

7.5. Physical Examinations

Physical examinations, including height and weight (to be measured at the screening visit only), will be performed at screening, and at follow-up. An abbreviated physical examination will be performed on visits 2 and 3. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event and reported as such.

Descriptive statistics for weight and height will be provided. Individual results will be presented in the subject data listings.

7.6. Vital Signs

Any vital sign that is judged by the investigator as clinically significant will be considered an adverse event and reported as such.

All individual vital signs results (pulse, systolic and diastolic BP, body temperature, and respiratory rate) will be listed.

Summary statistics for vital signs (pulse, systolic and diastolic BP, body temperature, and respiratory rate) in seated or supine position will be presented for screening, for visits 2 and 3, and for the follow-up visit. Vital signs values and changes from baseline to each visit and time point will be summarized using descriptive statistics. The incidence of potentially clinically

significant abnormal values will be summarized using subject counts and these values will be listed separately in the subject data listings.

Vital sign measurements will be present graphically for nominal measurements and change from baseline. Each graph will have measurement (e.g. systolic BP) per part of the study where y-axis is the measurement and x-axis is time. There will be a mean line with SD bars for each dose and each subject group (healthy subjects or HD patients).

Table 2 specifies the criteria for identifying vital signs as potentially clinically significant abnormal values. Note that in order to qualify as potentially clinically significant abnormal, a value needs to meet both criteria below: ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change relative to baseline column.

Table 2: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥15
	≤50 bpm	Decrease of ≥15
Systolic blood pressure	≥180 mm Hg	Increase of ≥20 mm Hg
	≤85 mm Hg	Decrease of ≥20 mm Hg
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15 mm Hg
	≤40 mm Hg	Decrease of ≥15 mm Hg

7.7. Electrocardiography

Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered an adverse event and reported as such.

Summary statistics for ECG measurements will be presented for screening, days -1 and 1 of visit 2 and days -1, 1 and 2 of visit 3, and for the follow-up visit. ECG variables will be averaged in case of repeated measurements in a single visit. ECG variable results and changes from baseline (Visit 2) to each visit and time point will be summarized using descriptive statistics and also presented graphically.

ECG measurements will be present graphically for nominal measurements and change from baseline. Each graph will have measurement (i.e. QT) per part of the study where y-axis is the measurement and x-axis is time. There will be a mean line with SD bars for each dose and each subject group (healthy volunteers or HD patients).

Shifts in ECG findings (normal and abnormal as evaluated by the investigator) from baseline to each visit and time point will be summarized using subject counts. For overall, the worst postbaseline finding (the abnormal finding if there are both normal and abnormal findings) for the subject will be summarized.

7.8. Concomitant Medications or Therapies

All concomitant medications will be coded using the WHODD.

Use of concomitant medication or treatment will be monitored throughout the study.

The incidence of concomitant therapies and medications will be summarized using descriptive statistics by therapeutic class category and preferred term. Subjects are counted only once in each therapeutic class, and only once in each preferred term category. Concomitant therapies and medications will include all medications up to the end of study as defined in the study protocol.

A medication is classified as concomitant medication if one of the following conditions is met:

- If the medication start date and the medication stop date is missing
- If the medication start date is known and medication stop date is missing and medication start date is less than or equal to the study medication last date and flag for continuation is yes.
- If the medication start date is missing and the medication stop date is known and is greater than or equal to the study medication first date
- If the medication start date and the medication stop date are both known and the medication start date is less than or equal to the study medication last date and the medication stop date is greater than or equal to the study medication first date.

The prior and concomitant medication or treatment used by HD patients will be listed only.

8. 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 by part and cohort in the disposition table.

9. PHARMACOKINETIC ANALYSIS

9.1. General

The pharmacokinetic analysis set will be used for all pharmacokinetic analyses. No formal statistical analyses of the pharmacokinetic data will be performed. All data will be listed and summarized descriptively by part and cohort and presented in tabular and graphical form where appropriate.

9.2. Pharmacokinetic Parameters

The following pharmacokinetic parameters will be determined or calculated from the plasma concentration-time data using non-compartmental analysis for pridopidine and its metabolite TV-45065, when possible. Actual sampling times will be used in the analysis.

Table 3: Pharmacokinetic Parameters

Parameter	Description	SAS Programming Notes
C_{max}	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	CMAX from WinNonlin® (WNL)
t_{max}	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	TMAX from WNL
AUC	All AUC values will be calculated using the linear up / log down method, expressed in units of concentration x time.	
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to 24 hours postdose.	AUC0_24 from WNL where partial time =24
AUC_{0-t}	Area under the plasma concentration-time curve (time 0 to time of last measurable analyte concentration).	AUCLAST from WNL
AUC_{0-inf}	Area under the plasma concentration-time curve (time 0 to infinity), calculated as: $AUC_{0-inf} = AUC_{0-t} + C_{tlast}/k_{el}$, where C_{tlast} is the last measurable analyte concentration.	AUCINF_obs from WNL
%AUC	Percentage of estimated part for the calculation of AUC_{0-inf}.	AUC_%Extrap_obs from WNL If AUC_%Extrap_obs > 20% then associated parameters (AUC_{0-inf}, k_{el}, $t_{1/2}$) are flagged
$t_{1/2}$	Terminal elimination half-life, calculated as $ln(2)/k_{el}$, expressed in time units.	HL_Lambda_z from WNL

Parameter	Description	SAS Programming Notes
V_d/F	Apparent volume of distribution of the drug following extravascular administration	Vz_F_obs from WNL

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.

9.3. Plasma Pharmacokinetic Analysis

9.3.1. Plasma Pharmacokinetic Concentrations

Plasma concentrations for pridopidine and its metabolite TV-45065 that are BQL of the assay will be substituted by half the lower limit of quantification (LLOQ) in the computation of mean concentration values. Missing values will be ignored when calculating mean concentrations. Descriptive statistics (n, mean, geometric mean, SD, CV, median, minimum, and maximum) will be used to summarize the plasma concentrations by part, cohort and nominal time point. If over half of the subjects at a given time point have values BQL then the descriptive statistics will not be presented and will instead display as BQL for the mean and missing for all other statistics (except the minimum and maximum value).

Linear and semi-logarithmic plots of the geometric mean plasma concentration by scheduled sampling time will be provided by part and cohort. These plots will show time in hours. The plots will match the summary table results and will not have an observation at a given time point if more than half of the subjects have values BQL.

Combined individual profiles of pridopidine and its metabolite TV-45065 in plasma by actual sampling time, showing all subjects in a single plot by part and cohort will be presented on both a linear and a semi-logarithmic scale (1 graph for each analyte and cohort).

Linear and semi-logarithmic plots of the individual plasma concentration of pridopidine and its metabolite TV-45065 by actual sampling time will be provided by subject. These plots will show time in hours. Individual plots will use the BQL handling procedure described below for "Pharmacokinetic Parameters".

All individual subject plasma concentration data for pridopidine and its metabolite TV-45065 will be listed by part, cohort and nominal time point.

9.3.2. Plasma Pharmacokinetic Parameters

The pharmacokinetic parameters will be estimated from the pridopidine and its metabolite TV-45065 (where data permit) plasma concentration-time profiles for all subjects in the pharmacokinetic analysis set. The concentration data as provided by the Bioanalytical Laboratory and (derived) actual blood sampling times will be used in the pharmacokinetic calculations.

In estimating the pharmacokinetic parameters, BQL values at time 0, at a sampling time before the first quantifiable plasma drug concentration will be treated as zero. All other BQL values will

be treated as missing. Missing values will be ignored when calculating pharmacokinetic parameters.

Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the pharmacokinetic parameter.

The terminal elimination rate constant (k_{el}) will be determined by plotting the concentration data versus time on a semi-logarithmic scale. The time interval of the terminal elimination phase will be determined by visual inspection. Linear regression on log-transformed concentrations within this interval will be used to calculate the terminal elimination rate constant. At least 3 non-BQL data points are required to retain a reliable k_{el} and associated parameters. Points prior to and including C_{max} will not be included in this interval. If the adjusted r^2 from the regression is ≤ 0.80 and the residual area of the $AUC_{0\text{-}inf}$ extrapolated is >20% then the associated pharmacokinetic parameters may be considered unreliable. The values will be included in the analysis, but will be flagged in the individual listing, accompanied by a footnote.

Descriptive statistics (n, mean, geometric mean, SD, CV, median, minimum, and maximum) will be used to summarize the calculated pharmacokinetic parameters by part and cohort. All individual pharmacokinetic parameters will be listed.

10. PHARMACODYNAMIC ANALYSIS

All pharmacodynamic analyses will be performed outside of the scope of this SAP and reported separately.

11. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The pharmacokinetic/pharmacodynamic analyses will be performed outside of the scope of this SAP. The pharmacokinetic/pharmacodynamic results will be analyzed and reported separately.

12. PHARMACOGENETIC AND BIOMARKER ANALYSIS

Results of the exploratory biomarker and pharmacogenetic analyses will be reported outside of the scope of this SAP and reported in a separate addendum report.

13. STATISTICAL SOFTWARE

All data listings, graphs, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

The pharmacokinetic parameters of pridopidine and its metabolite TV-45065 will be estimated using validated Phoenix™ WinNonlin®, Version 6.3 (Pharsight Corporation).

14. REFERENCES

Clinical study protocol. 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. Final with Amendment 01, Approval Date: 11 November 2016.

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.