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

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Statistical Analysis Plan

Study Number TV7820-CNS-20016

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

(Open PRIdopidine Dose Evaluation in Huntington's Disease)

Phase 2

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

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Sponsor

Teva Branded Pharmaceutical Products R&D, Inc.

[redacted]

Prepared by: [redacted]
Global Statistics

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: A Multi-Center, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Pridopidine in Patients with Huntington's Disease (Open PRIDE-HD)

Study Title: TV7820-CNS-20016

Statistical Analysis Plan for:

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

Version: Final

Date: 08- Jan-2018

Author: [redacted]
Global Statistics

Approver: [redacted] 1/11/2018
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Date

Approver: [redacted] 1/9/18
Senior Director, Clinical Development, Movement Disorders
Date

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
BMI	body mass index
CAG	Cytosine-Adenosine-Guanine
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
EoS	End of Study
HD	Huntington's disease
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mPPT	Modified Physical Performance Test
PBA-s	Problem-Behaviors Assessment-Short Form
PT	preferred term
Q-motor	Quantitative motor
R&D	Research and Development
SAP	statistical analysis plan
SD	Standard Deviation
SE	Standard Error
SF-12	Short Form 12
SMQ	Standard MedDRA Queries
SOC	system organ class
SOP	standard operating procedure
TC	telephone contact
TFC	Total Functional Capacity
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale
ULN	upper limit of normal
WHO	World Health Organization

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. study TV7820-CNS-20016 (A Multi-Center, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Pridopidine in Patients with Huntington's Disease (Open PRIDE-HD)), and was written in accordance with SOP GBP_RD_702 (Statistical Analysis Plan).

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 patient 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.

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Study Objectives

The primary objective of this study is to evaluate safety and tolerability of pridopidine in patients with Huntington's disease (HD)**.**

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

1.2. Study Endpoints

1.2.1. Safety Endpoints

The safety endpoints for this study are as follows:

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

1.2.2. Tolerability Endpoints

The tolerability endpoints for this study are as follows:

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

1.2.3. Efficacy Endpoints

Efficacy endpoints for this study include the following:

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

- Quantitative motor (Q-motor) assessments (up to 104 weeks; not applicable for newly enrolled patients after Global Amendment 02)

2. STUDY DESIGN

2.1. General Design

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

The assessments and procedures performed during each study visit are detailed in Section 3.12 of the protocol.

Up to 650 patients from the PRIDE-HD, Open PRIDE-HD, Open-HART, or future safety and efficacy clinical trials of pridopidine studies are planned to be enrolled to receive a total daily dose of 90 mg pridopidine (45 mg bid) for the duration of the study.

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

In addition, patients who have already completed their defined study period under Open PRIDE-HD global or local amendments and have discontinued treatment with pridopidine can be re-enrolled and re-enter the Open PRIDE-HD study. A repeat, 2nd screening and baseline visit will be scheduled after completion of the End of Study (EoS) visit. These patients will complete the repeated (2nd) screening and baseline visit assessments (including meeting all eligibility criteria, see procedures for V1 and V2), and undergo a 1-week titration period and resume attendance of the study visits from the point at which they exited.

All patients will be treated with study drug during the course of the study. After the 1 week titration period, patients will be seen at weeks 4, 12, 26, 52, 78, and every 26 weeks thereafter. An EoS follow-up visit will take place 2 weeks after end of treatment visit. Safety evaluation telephone calls will be performed at weeks 18, 38, and every 26 weeks thereafter. The alternating safety visits and telephone contacts (TCs) result in a safety assessment frequency of approximately every 3 months throughout the entire study duration. The safety TCs must be conducted by the study investigator. During these phone calls, inquiries about adverse events, concomitant medication (including changes in use of benzodiazepines and antidepressants), changes in use of alcohol and illicit drugs, C-SSRS, and an abbreviated PBA-s (a subset of PBA-s questions on depressed mood, suicidal ideation, anxiety, irritability, loss of motivation, and obsessive-compulsive behaviors) will be conducted.

During the TCs, if the patient receives a score of 0 on the C-SSRS and PBA-s suicidal ideation assessments, the subsequent safety TCs will remain as scheduled as long as the scores of 0 are unchanged. If the patient receives a score of 1 or 2 on the C-SSRS or PBA-s suicidal ideation assessments, the safety TCs will be conducted every 4 weeks to monitor the patient's status until the scores change to 0 (after which the frequency of safety TCs will revert back as scheduled, as described above). Patients with a C-SSRS ideation score of 3 and above or a PBA-s suicidality

score of 3 and above, and all patients with C-SSRS suicidal attempts or acts (behavior), will be discontinued from treatment with study medication and will be referred to a psychiatrist for further evaluation and assessment, and handled as described in Section 6.1.5. of the protocol.

For patients with a C-SSRS or PBA-s score of 1 or 2, if in the judgment of the investigator, the patient is not in good mental health during an in-clinic visit or safety TC, the frequency and the methods for monitoring may be changed (ie, more frequent visits or TCs may be added as deemed necessary, or the patient can be referred to a psychiatrist for additional evaluation and treatment and will be monitored until recovery or their condition stabilizes, in accordance with the instructions provided in Section 6.1.5 and Section 7.8.1 of the protocol.

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

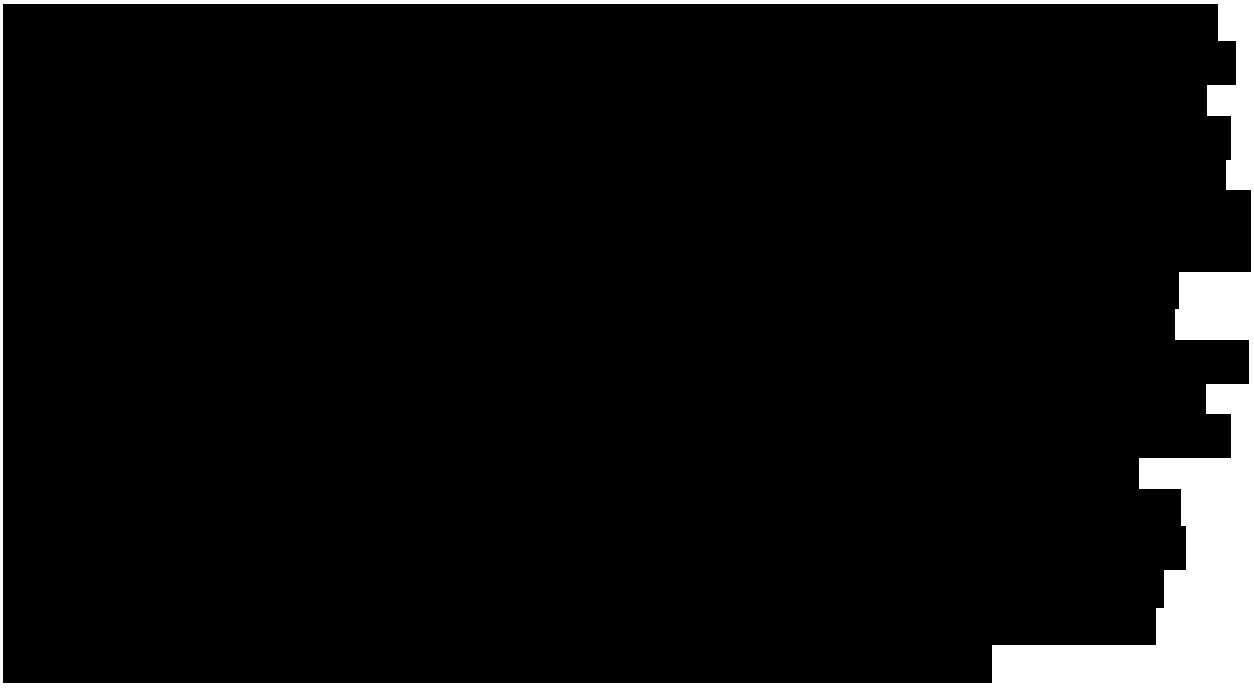
Patients who withdraw from the study will have the early termination procedures and assessments performed at their final visit.

An independent internal safety committee will oversee the study (see Section 3.6.1 of the protocol).

Digital Health Sub-study (optional participation):

Motor symptoms can be objectively assessed in HD patients using different quantitative motor assessments.

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



Study procedures and assessments are outlined in Table 1 of the sub-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

During the conduct of this study, an internal safety committee will review accumulating safety data on a regular basis (or adhoc if required, as detailed in the internal safety committee charter) to ensure the continuing safety of the study patients and study conduct issues. Additional details are outlined in Section 3.6.1 of the protocol.

2.4. Sample Size and Power Considerations

This is an open-label study. The sample size for this study is not based on statistical considerations; hence, only descriptive statistics will be presented. Up to 650 patients who completed the PRIDE-HD, exited from Open PRIDE-HD global or local amendments, completed any future safety and efficacy clinical trials of pridopidine, or transitioned from the ongoing Open-HART study and met patient exclusion/inclusion criteria will be enrolled.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

There will be no formal interim analysis for this study.

2.5.2. Final Analyses and Reporting

All analyses 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 to SOP GBP_RD_702 (Statistical Analysis Plan).

The data collected in the digital health sub-study will be analyzed and reported separately from this SAP by [redacted]

3. ANALYSIS SETS

3.1.1. Intent-to-Treat Analysis Set

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

3.1.2. Safety Analysis Set

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

3.1.3. Full Analysis Set

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

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. Descriptive statistics for categorical variables include patient counts and percentages, missing category will be displayed as appropriate.

4.2. Specification of Baseline Values

For patients from the PRIDE-HD study, the baseline value is the last observed data prior to the first dose of study drug in this study. For patients from the ACR16C015 (OpenHART) study, the baseline value is the last observed data prior to the first dose of study drug in the Open-HART study.

ECGs at screening are performed in triplicate. If the screening value has to be used for the baseline value for patients from the PRIDE-HD study, then for the ECG variables use the mean of 3 measurements as the baseline value. For the ECG finding, use "abnormal" as the baseline value if any of the responses are abnormal, and "normal" as the baseline value if all responses are normal.

4.3. Scoring for Rating Scales

A detailed description for all rating scales below can be found in the protocol.

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. The UHDRS-TMS is calculated as the sum of the 31 motor assessments.

The mPPT quantifies the patient's performance in physical tasks. It is a standardized 9-item test that measures the patient's performance on functional tasks. Both the speed and accuracy at which the patients complete the items are taken into account during scoring. The maximum score of the test is 36, with higher scores indicating better performance. The mPPT total score calculated as the sum of the 9 items. SeeAppendix A for details of the scoring method for the mPPT total score.

The TFC scale of the UHDRS assesses 5 functional domains associated with disability (occupation, finances, domestic chores, activities of daily living, and care level). Scores on each item range from 0 to either 2 or 3 (eg, Occupation: 0 = unable, 1 = marginal work only, 2 = reduced capacity for usual job, 3 = normal). The 5 items are summed to yield a TFC total score, which ranges from 0 to 13, with greater scores indicating higher functioning.

The SF-12® is a multipurpose short-form generic measure of health status. The 12 items in the SF-12® are a subset of those in the SF-36®; SF-12® includes 1 or 2 items from each of the 8 health concepts. The SF-12® total score is calculated as the sum of the 12 items.

The PBA-s is a brief semi-structured interview covering the most common behavioral and psychiatric manifestations of HD. The interview is not restricted to a single construct, but rather

covers several broad symptom domains relevant to HD, comprising 11 items. Each symptom is rated for both severity and for frequency on a 5-point scale. Severity and frequency scores are multiplied (after setting all values outside the range of 0-4 to missing) to produce an overall 'PBA score' for each symptom. The PBA total score is the sum of all PBA scores across the 11 symptoms.

Q-Motor assessments will be performed only in those sites that have access to the devices needed to perform the assessments and, where this is the case, only in those patients who are capable of performing the assessments. All Q-Motor assessments are based on the application of pre-calibrated and temperature-controlled force transducers and 3-dimensional position sensors with very high sensitivity and test-retest reliability across sessions and sites in a multicenter clinical study. If a certain test has a left and right value, an average value will be calculated from the test.

4.4. Handling Withdrawals and Missing Data

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

For the TMS component of the UHDRS, if responses to 1 assessment up to 25% of assessments are missing, the missing responses will be replaced by the average of the remaining responses within the TMS component. If responses to more than 25% of the assessments are missing, the missing responses will not be replaced and the UHDRS-TMS will be set to missing.

For mPPT, item 1 (balance tasks), item 4 (put on and remove a jacket), and item 6 (turn 360 degrees) have to be calculated before calculating the total score. For all 3 items, if any questions are missing then the missing responses will not be replaced and the item will be sets to missing. After calculating items 1, 4, and 6, if responses to 1 item up to 25% of items are missing, the missing responses will be replaced by the average of the remaining responses. If responses to more than 25% of the items are missing, the missing responses will not be replaced and the total score will be set to missing.

For the TFC scale of the UHDRS, if responses to 1 item up to 25% of items are missing, the missing responses will be replaced by the average of the remaining responses within the TFC scale. If responses to more than 25% of the assessments are missing, the missing responses will not be replaced and the UHDRS-TFC will be set to missing.

For SF-12, if responses to 1 item up to 25% of items are missing, the missing responses will be replaced by the average of the remaining responses. If responses to more than 25% of the items are missing, the missing responses will not be replaced and the total score will be set to missing.

For PBA-s, the severity x frequency items need to be calculated before calculating the total score. If either the severity or frequency value is missing then the item will be equal to the nonmissing value. After calculating the items, if responses to 1 item up to 25% of items are missing, the missing responses will be replaced by the average of the remaining responses. If responses to more than 25% of the items are missing, the missing responses will not be replaced and the total score will be set to missing.

For Q-motor assessments, if either the left or right value is missing for a certain test, then the average value will be equal to the nonmissing value.

4.5. Study Days and Visits

Study days are numbered relative to the first day of study drug administration. The start of treatment (Day 1) is defined as the date on which a patient takes the first dose of study drug, as recorded on the study drug diary. 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).

For efficacy and safety by-visit analyses, data collected at postbaseline scheduled visits will be included using their scheduled visit, data collected at postbaseline unscheduled visits will be included and assigned to their corresponding scheduled visit, and data collected at early termination visits will be included and assigned to the next scheduled visit. After the assignments are made, if there is a scheduled and unscheduled visit at the same visit, the scheduled visit will be used in the analysis.

5. STUDY POPULATION

5.1. General

The ITT analysis set will be used for all study population summaries. Summaries will be presented for all patients.

5.2. Patient Disposition

Patient screened, patients screened but not in the ITT analysis set (and reason not in the ITT analysis set) will be summarized using patient counts. Patients in the ITT analysis set, patients in the ITT analysis set but not treated, patients in the safety and full analysis sets, patients who completed treatment and completed study, and patients who withdraw from the treatment and study (and reasons for withdrawing) will be summarized using descriptive statisitcs.

5.3. Demographics and Baseline Characteristics

For demographics, the continuous variables of patient age, weight, height, and body mass index (BMI) will be summarized using descriptive statistics. The categorical variables of patient sex, race, and ethnicity will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

For baseline characteristics, the categorical variables of CYP2D6 metabolizer genotype (poor, extensive, intermediate or ultra-rapid metabolizer), neuroleptic use, and number of cytosine-adenosine-guanine (CAG) repeats, all determined from baseline in the PRIDE-HD or HART studies, will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

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 (PT). Patients are counted only once in each SOC category, and only once in each PT category.

5.5. Prior Therapy and Medication

Any prior therapy or medication a patient has had within 2 weeks prior to screening will be recorded on the CRF. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

The incidence of prior therapies and medications will be summarized using descriptive statistics by therapeutic class and PT. Patients are counted only once in each therapeutic class category, and only once in each PT category. Prior therapies and medications will include all medications taken and therapies administered before the first day of study drug administration.

5.6. Electrocardiography

ECG findings (normal and abnormal) at baseline will be summarized using descriptive statistics.

5.7. Study Protocol Violations

Data from patients with any protocol violations (as recorded in protocol violation CRF) during the study will be summarized overall and for each category using descriptive statistics.

6. EFFICACY ANALYSIS

6.1. General

The ITT analysis set will be used for all study population summaries unless otherwise noted. Summaries will be presented for all patients.

6.2. Efficacy Endpoint and Analysis

The efficacy endpoints are as follows:

- UHDRS-TMS change from baseline to each visit that this is measured.
- mPPT total score change from baseline to each visit that this is measured.
- UHDRS-TFC change from baseline to each visit that this is measured.
- SF-12 total score change from baseline to each visit that this is measured.
- PBA-s total score change from baseline to each visit that this is measured.
- Q-motor assessments (digitomotography, dysdiadochomotography, manumotography and choreomotography, and pedomotography) change from baseline to each visit that this is measured.

All efficacy endpoints wll be summarized for actual values and changes from baseline to each visit using descriptive statistics.

PBA-s domain scores will also be summarized for actual values and changes from baseline of this study to each visit using descriptive statistics.

No formal inferential statistics will be applied to the efficacy endpoints. Efficacy analyses will be considered exploratory.

7. SAFETY ANALYSIS

7.1. General

The safety analysis set will be used for all study population summaries unless otherwise noted. Summaries will be presented for all patients.

7.2. Duration of Exposure to Study Drug

Duration of exposure to study drug (days) for individual patients is the number of days patient received drug (last day of study drug – first day of study drug + 1). Duration of treatment (days) will be summarized using descriptive statistics. Weeks on treatment using the categories ≤4 weeks, >4 to ≤12 weeks, >12 to ≤26 weeks, >26 to ≤52 weeks, >52 to ≤78 weeks, >78 to ≤104 weeks, and >104 weeks will also be summarized using descriptive statistics.

7.3. Adverse Events

All AEs will be coded using the MedDRA. AEs occurring on or after the first day of study drug administration will be included in the summaries. Summaries will be presented for all AEs (overall and by severity), AEs determined by the investigator to be related to study drug (overall and by severity), serious AEs, AEs leading to withdrawal from the study, and non-serious AEs.

The incidence and total number of AEs will be summarized using descriptive statistics by SOC and PT (all AEs overall will also be presented by just PT category). For the incidence of AEs, patients are counted only once in each SOC category, and only once in each PT category. The exposure adjusted incidence rate will also be presented and is defined as the number of patients with an AE divided by patient-years of treatment. For calculating patient-years, patients with an AE contribute with treatment exposure up to the day of their first AE, and patients without an AE contribute with the entire treatment exposure. For the summary by severity, patients are counted at the greatest severity. AEs missing relationship to study drug will be included in the study drug related summary.

7.4. Clinical Laboratory Tests

Laboratory test results will be presented in standard international (SI) units.

Summary statistics for serum chemistry, hematology, and urinalysis laboratory tests will be presented at baseline and each visit. Laboratory tests values and changes from baseline to each visit will be summarized using descriptive statistics.

Shifts (below, within, and above the normal range) from baseline to each visit will be summarized using patient counts.

The incidence of potentially clinically significant abnormal values will be summarized for laboratory tests using descriptive statistics with the criteria specified in Table 1. These summaries willl include all postbaseline values (including scheduled, unscheduled, and early termination visits).

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
	Women	≥506 μmol/L
Bilirubin (total)		≥34.2 μmol/L
Hematology		
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L
Hemoglobin	Men	≤115 g/L
	Women	≤95 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
Total protein		≥2 unit increase from baseline

ULN=upper limit of normal

7.5. Vital Signs

Summary statistics for pulse, blood pressure (supine/sitting and standing), body temperature, weight, and orthostatic blood pressure (supine/sitting – standing value) will be presented at baseline and each visit. Vital signs values and changes from baseline to each visit will by summarized using descriptive statistics.

The incidence of potentially clinically significant abnormal values will be summarized for vital signs using descriptive statistics with the criteria specified in Table 2. These summaries willl include all postbaseline values (including scheduled, unscheduled, and withdrawal visits). 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
	≤90 mm Hg	Decrease of ≥20
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15
	≤50 mm Hg	Decrease of ≥15
Body temperature	≥38.3°C	Change of ≥1.1°C
Orthostatic SBP (mmHg)	>= 20 mmHg	
Orthostatic DBP (mmHg)	>= 10 mmHg	

7.6. Electrocardiography

Shifts (normal and abnormal) from baseline to overall finding and each visit willl be summarized using patient counts. For overall finding, the summary will use the worst postbaseline finding for the patient (the abnormal finding if there are both normal and abnormal findings). Summary statistics for ECG variables will be presented at baseline and each visit. Actual values and changes from baseline to each visit will be summarized using descriptive statistics.

The incidence of potentially clinically significant abnormal values for ECG variables will be summarized using descriptive statistics with the criteria specified below.

- QTcF values >450 msec or >480 msec or >500 msec.
- QTcF change from baseline values >30 or >60.
- PR change from baseline ≥25% and value >200.
- QRS change from baseline ≥25% and value >110.
- Heart rate value <60 bpm or >100 bpm.

7.7. Concomitant Medications or Therapies

Concomitant medications and therapies, including medications that are taken on an as needed basis and occasional therapies, will be monitored during the study. All concomitant medications will be coded using the WHO drug.

The incidence of concomitant medications and therapies will be summarized using descriptive statistics by therapeutic class category and PT. Patients are counted only once in each therapeutic class, and only once in each PT category. Concomitant medications and therapies will include all medications taken and therapies administered from the first day of study drug administration up to the end of study as defined in the study protocol.

7.8. Other Safety Assessments

Summary statistics for the C-SSRS baseline version will be presented at screening. Patients with suicidal ideation and behavior items will be summarized as categorical data using descriptive statistics.

Summary statistics for the C-SSRS last visit version will be presented at overall postbaseline. Patients with suicidal ideation and behavior items will be summarized as categorical data using descriptive statistics.

8. TOLERABILITY VARIABLES AND ANALYSIS

Tolearbility is summarized with the safety analysis.

9. STATISTICAL SOFTWARE

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

10. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

There are no changes to analyses specified in the study protocol.

APPENDIX A. MODIFIED PHYSICAL PERFORMANCE TEST (MPPT) SCORING METHOD

No.	Task	Items Score Values
1.	Balance Tasks	**Standing Balance Feet Together** • ≥ 10 sec = 1 • 0 - <10 sec or Unable = 0
		Standing Balance Semi Tandem • ≥ 10 sec = 1 • 0 - <10 sec or Unable = 0
		Standing Balance Tandem • ≥ 10 sec = 2 • 3 – <10 sec = 1 • 0 - <3 sec or Unable = 0
2.	Chair rise	• >0 - 11 sec = 4 • >11 - 14 sec = 3 • >14 - 17 sec = 2 • >17 sec = 1 • 0, Unable = 0
3.	Lift a book and put it on a shelf	• >0 - 2 sec = 4 • >2 - 4 sec = 3 • >4 - 6 sec = 2 • >6 sec = 1 • 0, Unable = 0
4.	Put on and remove a jacket (sum of time to put and to remove the jacket)	• >0 - 10 sec = 4 • >10 - 15 sec = 3 • >15 – 20 sec = 2 • >20 sec = 1 • 0, Unable = 0
5.	Pick up a penny from floor	• >0 - 2 sec = 4 • >2 - 4 sec = 3 • >4 - 6 sec = 2 • > 6 sec = 1 • 0, Unable = 0
6.	Turn 360 degrees	**Steps** • Continuous = 2 • Discontinuous = 0
		Steadiness • Steady = 2 • Unsteady (grabs, staggers) = 0
7.	50-foot walk test	• >0 - 15 sec = 4 • >15 - 20 sec = 3 • >20 - 25 sec = 2 • >25 sec = 1 • 0, Unable = 0

8.	Climb one flight of stairs	• >0 - 5 sec = 4 • >5 - 10 sec = 3 • >10 – 15 sec = 2 • >15 sec = 1 • 0, Unable = 0
9.	Climb 4 flights of stairs (Number of flights climbed up and down)	• 4 flights = 4 • 3 flights = 3 • 2 flights = 2 • 1 flights = 1 • Unable = 0
	Total mPPT Score	**Sum of all Item score values [0-36]**