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Statistical Analysis Plan

Study Number ACR16C015

A multi-center, North American, open-label extension study of pridopidine (ACR16) in the symptomatic treatment of Huntington's Disease (Open-HART)

Phase 2

IND number: 77,419

Approval Date: 11 January 2018

Sponsor

Teva Branded Pharmaceutical Products R&D, Inc.

[redacted]

United States

Prepared by: [redacted]
Global Statistics

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: A multi-center, North American, open-label extension study of pridopidine (ACR16) in the symptomatic treatment of Huntington's Disease (Open-HART)

Study Title: ACR16C015

Statistical Analysis Plan for:

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

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[redacted]
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[redacted]
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Senior Director, Clinical Development, Movement Disorders
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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
FA	Functional Assessment
IS	Independence Scale
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PBA-s	Problem-Behaviors Assessment-Short Form
PT	preferred term
R&D	Research and Development
SAP	statistical analysis plan
SD	Standard Deviation
SE	Standard Error
SOC	system organ class
SOP	standard operating procedure
TFC	Total Functional Capacity
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale
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 ACR16C015, (A multi-center, open-label extension study of pridopidine (ACR16) in the symptomatic treatment of Huntington's Disease (Open-HART)), 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 (e.g. 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

The objective is to access the long-term safety of pridopidine and to analyze treatment affects during long-term, open-label treatment.

The primary objective of this study is to evaluate the long-term safety of pridopidine treatment and to collect information on Unified Huntington's Disease Rating Scale (UHDRS) development during long-term, open-label treatment.

2. STUDY DESIGN

2.1. General Design

Note: the SAP is based on Protocol Am 04 (dated 25 August 2016), and that Protocol Am 05 was issued (on 29 June 2017) for study virtualization but was not implemented.

This is a multi-center open-label study of pridopidine 45mg bid for patients who completed the ACR16C009 (HART) or TV7820-CNS-20002 (PRIDE-HD) studies.

At the **Baseline Visit** the following tests will be performed and documented: review and completion of informed consent; review of inclusion and exclusion criteria; pregnancy test (for females of childbearing potential); review of (baseline) adverse events (AEs), concomitant medication and medical history. All patients will be assessed for suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS). Evaluation for Research Study Consent and blood draw (calcium, magnesium, potassium, and creatinine for creatinine clearance calculation) will be performed for patients from the PRIDE-HD study.

The following assessments will be performed: physical examination including vital signs (heart rate and blood pressure) and weight; review of concomitant medication; (including inquiry about changes in use of benzodiazepines and antidepressants); inquiry about changes in use of alcohol and illicit drugs; UHDRS (including motor assessment, cognitive assessment, behavioral assessment, functional capacity, independence scale, functional assessment); 12-lead electrocardiogram (ECG) (single).

Trial medication will be dispensed and an appointment made for the next visit.

At **Telephone Visit 1 (T1, Week 1)** an evaluation for research study consent will be conducted, any AEs will be collected and reported, compliance will be confirmed, concomitant medication reviewed (including inquiry about changes in use of benzodiazepines and antidepressants); inquiry about changes in use of alcohol and illicit drugs, C-SSRS, abbreviated Problem-Behaviors Assessment-Short Form (PBA-s), and an appointment for next contact will be made. Evaluation for Research Study Consent will be performed for patients from the PRIDE-HD study.

At **Visit 1 (1 Month)** the following will be documented: an evaluation for research study consent, review of concomitant medications (including inquiry about changes in use of benzodiazepines and antidepressants); inquiry about changes in use of alcohol and illicit drugs, AEs, C-SSRS, PBA-s, vital signs and drug compliance. Evaluation for Research Study Consent, ECG and blood draw (calcium, magnesium, potassium, and creatinine for creatinine clearance calculation) will be performed for patients from the PRIDE-HD study.

Subsequently, the patient will be contacted every 3 months as per below:

At **Telephone or in-person Visits [Safety Visit (SV)] (eg after 3, 9, 15 months etc.)** the following will be documented: an evaluation for research study consent, review of concomitant medication (including inquiry about changes in use of benzodiazepines and antidepressants); inquiry about changes in use of alcohol and illicit drugs, C-SSRS and PBA-s assessment, review of AEs, and assessment of compliance with trial medication. A 12-lead ECG will be obtained, vital signs will be assessed and calcium, magnesium and potassium level and creatinine for

creatinine clearance calculation will be drawn [hypokalemia is defined as a potassium level less than 3.5 mEq/L)]. If less than 3.5 mEq/L, patient's study drug will be suspended until normal (greater than or equal to 3.5mEq/L). Participants can choose to have the assessments of vital signs, ECG and blood draw for calcium, magnesium, potassium, and creatinine for creatinine clearance calculation performed by their GP and/or local cardiologist or schedule a visit with site but the site must have a telephone contact with the participant to review concomitant medication, AEs and assess compliance with trial medication.

At **Telephone contacts [C] (eg once a month between on-site visits)** the following will be documented: an evaluation for research study consent, review of concomitant medication (including inquiry about changes in use of benzodiazepines and antidepressants); inquiry about changes in use of alcohol and illicit drugs, review of adverse events, C-SSRS and an abbreviated PBA-s assessment.

At **Clinic Visits (eg 6, 12, 18 months etc.)** the following tests will be performed and documented: an evaluation for research study consent, brief physical examination including vital signs and weight, calcium, magnesium, and potassium levels and creatinine for creatinine clearance calculation will be drawn [hypokalemia is defined as a potassium level less than 3.5 mEq/L)]. If less than 3.5 mEq/L, patient's study drug will be suspended until normal (greater than or equal to 3.5mEq/L), review of concomitant medication (including inquiry about changes in use of benzodiazepines and antidepressants); inquiry about changes in use of alcohol and illicit drugs, review of AEs, C-SSRS, PBA-s, 12-lead ECG and assessment of compliance with trial medication. On a yearly basis, UHDRS (including motor assessment, cognitive assessment, behavioral assessment, functional capacity, independence scale, functional Assessment) and a pregnancy test (for females of childbearing potential) should be done. The PBA-s will be collected at all safety and clinic visits except on those at which the UHDRS is performed.

Withdrawal from treatment

If the patient wishes to stop the drug, or is judged by the investigator to not be suitable for continued therapy, or the study is discontinued, a clinic visit ("withdrawal visit", end of study drug visit) should be performed and the patient withdrawn from the study. A (telephone) follow-up visit (30 d TC F/U) to collect and report AEs (as well as inquiry about changes in use of benzodiazepines and antidepressants, and inquiry about changes in use of alcohol and illicit drugs), C-SSRS and an abbreviated PBA-s assessment should take place one month after the actual discontinuation of study drug took place.

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.

Unscheduled Visit(s)

If a patient has tolerability problems, or has to de-escalate the investigational treatment, the investigator can decide to call the patient to an unscheduled study visit at the study center. Where a patient attends an Unscheduled Visit between the scheduled visits they should be instructed to attend their next visit according to the study schedule as planned.

Schedule of assessments are outlined in Table 1.2 of the protocol.

2.2. Efficacy Measures

- Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS)
- Unified Huntington's Disease Rating Scale – Total Functional Capacity (UHDRS-TFC)
- Unified Huntington's Disease Rating Scale – Functional Assessment (UHDRS-FA)
- Unified Huntington's Disease Rating Scale – Independence Scale (UHDRS-IS)
- UHDRS Behavioral Assessment
- UHDRS Cognitive Assessment
- PBA-s (also part of safety measures)

2.3. Safety Measures

- AEs
- Vital signs assessments
- ECG findings
- Concomitant medication usage.
- Physical examination findings
- Suicidality (C-SSRS and PBA-s)

2.4. Randomization and Blinding

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

2.5. Sample Size and Power Considerations

As this is an open-label extension study, no sample size calculations have been performed. Patients who completed the HART or the PRIDE-HD study and met patient exclusion/inclusion criteria will be enrolled.

2.6. Sequence of Planned Analyses

2.6.1. Planned Interim Analyses

There will be no formal interim analysis for this study.

2.6.2. 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).

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.

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

The baseline value is the last observed data prior to the first dose of study drug in this study.

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 TFC scale of the UHDRS assesses 5 functional domains associated with disability (occupation, finances, domestic chores, activities of daily living, and care level). The UHDRS-TFC is calculated as the sum of the 5 functional capacity items.

The FA component of the UHDRS assesses 25 items associated with functional problems. The UHDRS-FA is calculated as the sum of the 25 items.

The behavioral assessment of the UHDRS comprises 11 items that measures the frequency and severity of symptoms related to affect, thought content and coping styles. Severity and frequency scores are multiplied (after setting all values outside the range of 0-4 to missing) to produce an overall score for each item. The total behavioral score is the sum of the overall scores across the 11 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 severitiy and for frequency. 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.

4.4. Handling Withdrawals and Missing Data

For all variables, only the observed data from the patients will be used in the statistical analyses, ie, 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 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 the FA 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 FA component. If responses to more than 25% of the assessments are missing, the missing responses will not be replaced and the UHDRS-FA will be set to missing.

For the behavioral assessment of the UHDRS and the 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.

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.

For socio-economics, the continuous variables of year of education, years in occupation most of career, years in current occupation, and number of times married will be summarized using descriptive statistics. The categorical variables of occupation most of career, current occupation, marital status, and handedness 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 prior to screening will be recorded on the case report form (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. Physical Examinations

Physical examination abnormal findings at baseline will be summarized using descriptive statistics.

5.8. 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 full analysis set 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.
- UHDRS-TFC change from baseline to each visit that this is measured.
- UHDRS-FA change from baseline to each visit that this is measured.
- UHDRS-IS change from baseline to each visit that this is measured.
- UHDRS Behavioral total score change from baseline to each visit that this is measured.
- UHDRS Cognitive tests change from baseline to each visit that this is measured.
- PBA-s total score 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.

UHDRS Behavioral domain scores and the 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. Years on treatment using the categories ≤1 year, >1 to ≤2 years, >2 to ≤3 years, >3 to ≤4 years, >4 to ≤5 years, >5 to ≤6 years, and >6 years 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.

In addition, a summary of AEs by time period of treatment will be presented.

7.4. Vital Signs

Summary statistics for pulse, blood pressure, body temperature, and weight 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 1. 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 1: 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

7.5. 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 criterian specified below.

- QTcF values >450 ms or >480 ms or >500 ms.
- 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.

7.6. Physical Examinations

Shifts (normal and abnormal) from baseline to each visit for each category will be summarized using patient counts.

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. STATISTICAL SOFTWARE

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

9. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

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