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

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CLINICAL STUDY PROTOCOL WITH AMENDMENT 05

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

SPONSOR TRIAL CODE: ACR16C015

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Central Electrocardiogram
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Central Laboratory
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Data Management
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PROTOCOL APPROVAL SHEET

TRIAL CODE	ACR16C015
PROTOCOL TITLE	A multi-center, North American, open-label extension study of pridopidine (ACR16) in the symptomatic treatment of Huntington's Disease (Open-HART)
APPROVERS(S)	[redacted] Senior Director, Therapeutic Area Head, Movement Disorders Teva Branded Pharmaceuticals [redacted] (Signature) Jun 29, 2017 (Date) Principal Investigator [redacted] University of Rochester [redacted] (Signature) 7/10/17 (Date)

THIS SHEET MUST BE ATTACHED TO THE PROTOCOL.

1 TABLE OF CONTENTS

1.1 Protocol Synopsis

TITLE	**A multi-center, North American, open-label extension study of pridopidine (ACR16) in the symptomatic treatment of Huntington's disease (Open-HART).**
PHASE	II
OBJECTIVES	The objective is to assess the long-term safety of pridopidine and to analyze treatment effects during long-term, open-label treatment. The primary objective is to assess the long-term safety of pridopidine treatment and to collect information on UHDRS development during long-term, open-label treatment. The exploratory objective is to evaluate patient and site staff satisfaction with virtual study visits and remote assessments administered in adult patients with Huntington's disease (HD).
STUDY DURATION	The study will continue until: • the investigational medicinal product (IMP) has been authorized for marketing by the respective regulatory authority in Canada or the USA; or • the study is discontinued for medical/scientific (risk-benefit) or commercial reasons.
STUDY DESIGN	Multi-center, open-label study of pridopidine 45 mg bid for patients who completed the HART (ACR16C009) or PRIDE-HD (TV7820-CNS-20002) studies and who transitioned from the Open-HART pre-virtualization study period.
NUMBER OF PATIENTS	47
INCLUSION AND EXCLUSION CRITERIA	**Inclusion criteria** • Patient is able to and has provided written Informed Consent prior to all study-related procedures. • [Revision 1] Patient has completed the HART (ACR16C009) or the PRIDE-HD (TV7820-CNS-20002) studies and had remained on IMP during the full on-treatment part of the study (including de-escalated patients) or has transitioned from the Open-HART pre-virtualization study period. • Patient is willing and able to take oral medication and able to comply with the study specific procedures. • Patient is not participating in another clinical study of an investigational intervention. • [New criterion] Patient has a wireless internet connection at home (and/or applicable locations) at the first remote visit. • [New criterion] Patient has the ability to transition from in-person study visits to virtual study visits. The first remote visit will take place within approximately 30 days after the last in-person visit. **Exclusion criteria** • [Revision 1] Ongoing treatment with tetrabenazine or deutetrabenazine, seizure threshold lowering medications,

	or certain antipsychotics and antidepressants (see Protocol Section 5.7 and current Operations Manual for list of disallowed medications). • [Revision 2] Newly instigated or changed treatment with neuroleptics/anti-psychotics. • [Revision 3] Use of tricyclic antidepressants or class I & III antiarrhythmics at any time during the study period. • [Revision 4] Any clinically significant, abnormal laboratory result, including clinically significant hepatic or renal impairment, or any ongoing adverse event (AE) that, in the opinion of the investigator (or qualified designee), affects the patient's suitability for the study or puts the patient at risk if he/she continues in the study. • [Revision 5] A prolonged QTc interval at the first remote visit (defined as a QTcF interval of >450 ms for both males and females using Fredericia's formula) or other clinically significant heart conditions as judged by the investigator (or qualified designee). • [Revision 6] Severe intercurrent illness that, in the opinion of the investigator (or qualified designee), may put the patient at risk when continuing participation in the study. • [Revision 7] Alcohol and/or drug abuse as defined by Diagnostic and Statistical Manual - Fourth Edition - Text Revision criteria for substance abuse – this includes the illicit use of cannabis. • Patients with AEs of suicidal ideation or attempt at any time in the past or as measured by a suicide ideation score of ≥3 on the Columbia-Suicide Severity Rating Scale (C-SSRS) (who answer "Yes" to questions 3, 4, and 5 in the scale suicidal ideation section), or a score of ≥3 on the Problem Behaviors Assessment – Short Form (PBA-s), or patients who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior), if an attempt or acts were performed at any time in the past, or patients who, in the opinion of the investigator (or qualified designee), present a risk of suicide. • Patients with a known history of epilepsy or a history of febrile seizure(s) or seizure(s) of unknown cause. • Females who are pregnant or lactating. • Females who are of child-bearing potential and not taking adequate contraceptive precautions (either oral, barrier, or chemical contraceptives) are excluded from the study. Females of child bearing potential taking acceptable contraceptive precautions can be included. • Known allergy to any ingredients of the study medication (Please refer to the Investigator Brochure (IB) for a full ingredient list). • [Revision 8] Creatinine clearance <60 mL/min at Virtual Transition Visit (VTV), calculated using the Cockcroft-Gault equation: (140-age) x mass (kg) x [0.85 if female]/72 x serum creatinine (mg/dL). It is allowed to repeat the test once, if clinically appropriate.

TREATMENT:	Pridopidine 45 mg twice daily (bid) – two active 45 mg capsules taken as two separate doses (90 mg pridopidine per day).
ADMINISTRATION	Oral. Capsules will be swallowed whole with water. One capsule should be taken early in the morning and one in the afternoon 7 to 10 hours after the morning dose, irrespective of food. Dose frequency de-escalation to one morning capsule only is permitted if tolerability issues arise. Subsequent re-escalation to twice-daily dosing may take place.
PROCEDURE	The signing of informed consent and the **VTV** will be held at the time of the patient's last in-person Open-HART study visit and within 30 days prior to the first remote visit (RV1). Patients may not transition from in-person visits to remote visits before signing informed consent. After signing informed consent and confirmation of the ability to perform virtual study visits, patients will transition from in-person study visits to remote visits in the Open-HART study. During the VTV the patient will be asked to appoint a research proxy (see Section 9.2). IMP will be dispensed at the VTV. All subsequent IMP dispensation will be shipped directly to the patient. Investigators (or qualified designees) will be trained on video conferencing equipment and remote connection techniques for administration of assessments prior to the patient's first test connection. Patients will be provided with a tablet for remote video conferencing visits after they have completed their last in-person visit and provided written informed consent. A test connection will be completed at the patient's home (and/or applicable location) by the vendor prior to the first remote visit to ensure that the investigational site and patient video conferencing equipment are working properly. The **first remote visit (RV1)** is to be completed within 30 days of the VTV. This visit will be the first virtual visit of the study and will be completed via a remote video conference. Safety and tolerability will be assessed at all visits of treatment until the end of patient participation, including the follow-up and End-of-Study (EOS) visits. Assessments will be performed according to Section 1.3. Additional **remote video visits** will be performed at Weeks 26, 52, and every 26 weeks thereafter (as well as for unscheduled visits [USVs]) until study discontinuation. During these virtual visits, inquiries about AEs, concomitant medication (including changes in use of benzodiazepines and antidepressants), changes in use of alcohol and drugs associated with substance abuse (legal or illicit), an evaluation for research study consent, C-SSRS collection, abbreviated PBA-s collection, and

	the Unified Huntington's Disease Rating Scale (UHDRS) will be conducted by the investigator (or qualified designee). The UHDRS will only be collected at virtual visits every 52 weeks and at EOS/ET or USVs. The abbreviated PBA-s will be collected at visits when the UHDRS (Behavior) is not collected. Remote video visits will be accompanied by an in-person visit from a mobile nurse (within 7 days). Mobile nurses will perform safety laboratory tests, pregnancy tests, vital sign measurements, electrocardiograms, weight, and study drug accountability at the patient's residence (and/or other applicable location) at the time points listed in Section 1.3. Safety evaluation **telephone contacts (TCs)** will be conducted by the investigator (or qualified designee) between remote visits at Weeks 13, 39, 65, 91, and every 13 weeks thereafter as well as at unscheduled visits (USVs). During these TCs, inquiries about AEs, concomitant medications (including changes in use of benzodiazepines and antidepressants), changes in use of alcohol and drugs associated with substance abuse (legal or illicit), an evaluation for research study consent, C-SSRS collection, and an abbreviated PBA-s collection will be conducted by the investigator (or qualified designee). The investigator (or qualified designee) will also discuss study drug compliance with the patient during each TC. Assessments will be collected according to Section 1.3. Patients who discontinue IMP due to safety or tolerability reasons, or the inability to complete virtual visits, may remain enrolled in the study without treatment at the discretion of the investigator (or qualified designee). Patients should complete the end-of-treatment **(EOT) visit** and continue with scheduled visits and assessments until the EOS or early termination (ET). Patients who complete all scheduled visits (remote video and TC) will have procedures and assessments performed via remote video conference and mobile nurse visit at the EOS/ET visit. Patients who withdraw from the study before completing the treatment period will have the EOS visit (or ET) procedures and assessments performed at his/her final visit. The end of study is defined as the last visit of the last patient. All patients will be followed for safety via TCs. **Withdrawal from treatment** If the patient wishes to stop treatment, is judged by the investigator (or qualified designee) to not be suitable for continued therapy, or the study is discontinued, a remote visit ("withdrawal visit", ET visit) should be performed and the patient withdrawn from the study. A (telephone) follow-up visit (30 d TC follow-up) to collect and report AEs, concomitant

	medications (as well as inquiry about changes in use of benzodiazepines and antidepressants), changes in use of alcohol and drugs associated with substance abuse (legal or illicit), C-SSRS, and an abbreviated PBA-s assessment should take place 1 month after the actual discontinuation of IMP took place. Additional criteria for discontinuation of IMP for individual patients are detailed in Section 7.7.1. Patients who discontinue IMP due to safety or tolerability reasons may continue in the study off-IMP and perform the scheduled visits and assessments. **Unscheduled visits** may occur as needed and can be completed via remote video, in-person visit, or TC (TC will be the primary form of contact; remote video or in-person visits may be scheduled at the discretion of the investigator [or qualified designee]). An USV may be used to perform assessments per the investigator's (or qualified designee's) judgement. An USV may also be used to re-consent a patient if necessary. If patients have concerns about the virtual nature of site visits, they may request an USV at the investigational center. The medical monitor will review individual requests and may approve 1 site USV per patient, per year. The assessments at site USVs will mirror those obtained during safety evaluation TCs (see Section 4.6.4). The investigator (or qualified designee) may schedule additional site visits on a case-by-case basis for patients that require closer monitoring due to safety events. If a patient has tolerability problems or has to de-escalate the investigational treatment, the investigator (or qualified designee) can decide to call the patient to an unscheduled study visit at the investigational center. Patients should be advised that if tolerability problems continue, then they should contact their investigator (or qualified designee) who may then withdraw them from the IMP (EOT visit) (see Section 7.7.2). If a patient attends an USV between the scheduled visits, they should be instructed to attend their next visit according to the study schedule as planned. The study will be carried out in accordance with the study protocol, guidelines on the International Conference of Harmonization for Good Clinical Practice, appropriate Food and Drug Administration Code of Federal Regulations, and local regulatory requirements. During the conduct of this study, an Internal Safety Committee will review accumulating safety data on a quarterly basis (or

	meet ad-hoc if a safety concern arises, as detailed in the Internal Safety Committee charter), to ensure the continuing safety of the study patients and study conduct issues. Patients excluded from the study due to lack of internet connection or inability to transition from in-person study visits to virtual study visits may be eligible to enroll in the Open-PRIDE-HD study (Study TV7820-CNS-20016).
STATISTICS	All reported adverse drug reactions will be tabulated. Safety statistics will be descriptive only.

1.2 Schedule of Assessments – Prior to Study Virtualization

1.3 Schedule of Assessments – Following Study Virtualization

Study Period	Treatment Period										EOT[1]	EOS[2]/ET	F/U	USV[3,4]
Visit Number		RV1	TC1	RV2	TC2	RV3	TC3	RV4	TC4	RV5	RV	RV	TC	RV/TC
Study Procedures and Assessments	VTV	Within 30 days of VTV	Week 13 (±14 days)	Week 26 (±14 days)	Week 39 (±14 days)	Week 52 (±14 days)	Week 65 (±14 days)	Week 78 (±14 days)	Week 91 (±14 days) and every 13 weeks (±14 days) thereafter	Week 104 (±14 days) and every 26 weeks (±14 days) thereafter	Week X (±Y days)	Week X (±Y days)	Week X (±30 days)	Week X (±Y days)
Remote Visit		X		X		X		X		X	X	X		X
Telephone Contact			X		X		X		X				X	X
Informed Consent[5]	X													X[6]
Designation of Research Proxy	X													
Updated Medical History	X[7]													
Eligibility Criteria	X	X												
Evaluation for Research Study Consent	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Test Connection[8]	X													
Mobile Device Kit	X											X		
Training Review	X													
Concomitant Medication Inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Benzodiazepines and Antidepressants Inquiry[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alcohol/Illicit Drug use Inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X													
Weight	X	X		X		X		X		X	X	X		X
Vital Signs (HR, BP)[10 11]	X	X		X		X		X		X	X	X		X
12-lead ECG[12]	X	X		X		X		X		X	X	X		X
Pregnancy Test[13]	X	X				X				X	X	X		X
Safety Laboratory Tests[10,14]	X	X		X		X		X		X	X	X		X
Creatinine Clearance Calculation[15]	X	X		X		X		X		X	X	X		X
UHDRS[16]	X	X				X				X	X	X		X
AE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Treatment Period										EOT[1]	EOS[2] /ET	F/U	USV [3,4]
Visit Number		RV1	TC1	RV2	TC2	RV3	TC3	RV4	TC4	RV5	RV	RV	TC	RV/ TC
Study Procedures and Assessments	VTV	Within 30 days of VTV	Week 13 (±14 days)	Week 26 (±14 days)	Week 39 (±14 days)	Week 52 (±14 days)	Week 65 (±14 days)	Week 78 (±14 days)	Week 91 (±14 days) and every 13 weeks (±14 days) thereafter	Week 104 (±14 days) and every 26 weeks (±14 days) thereafter	Week X (±Y days)	Week X (±Y days)	Week X (±30 days)	Week X (±Y days)
C-SSRS[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Abbreviated PBA-s[18]			X	X	X		X	X	X				X	
Satisfaction Survey[19]		X		X		X		X		X	X	X		
Dispense IMP and Instructions[20]	X			X	X	X	X	X	X	X				X
IMP Accountability[21]	X	X		X		X		X		X	X[21]	X[21]		
IMP Compliance	X	X	X	X	X	X	X	X	X	X	X	X		X

[1] This visit will be undertaken in place of the Early Termination visit when a patient is no longer able to receive IMP for various reasons but wishes to remain in the study. Patients who discontinue IMP due to safety or tolerability reasons, or the inability to complete virtual visits, may remain enrolled in the study without treatment at the discretion of the investigator (or qualified designee). Patients should complete the EOT visit and continue with scheduled visits and assessments until the EOS or ET. For subsequent visits, these patients will follow the Schedule of Assessments for the remaining remote video/mobile nurse and safety evaluation telephone contact visits.
[2] EOS is defined as the last visit of the last patient. All devices will be returned to the investigational center or vendor at the end of the study.
[3] An USV may be performed at any time during the study as deemed necessary by the investigator (or qualified designee). The date and reason for an USV will be recorded. Reasons for USVs may include, but are not limited to, need for blood draw for safety labs, a potential severe side effect, worsening of symptoms, etc. The following assessments are required at an USV: AE review and concomitant medication inquiry. Other assessments to be done at the discretion of the investigator (or qualified designee). The primary form of contact will be a TC, but video assessments and in-person visits may be scheduled at the discretion of the investigator (or qualified designee).
[4] For patients with concerns about the virtual nature of site visits, 1 site USV per year may take place at the investigational site that follows the assessments required for the safety evaluation TCs. The medical monitor will review individual requests for site visits and approve visits if deemed necessary. The investigator (or qualified designee) may schedule additional site visits on a case-by-case basis for patients that require closer monitoring due to safety events.
[5] Patients will complete the informed consent at their last in-person Open-HART study visit/VTV.
[6] An USV may also be scheduled to re-consent patients (if necessary).
[7] Medical history collected prior to study virtualization will remain in a separate database while updated medical history will be collected at VTV.
[8] Test connections are to be completed at home (and/or applicable location) by the vendor prior to the first remote visit to ensure remote video conferencing equipment functionality.
[9] Information on benzodiazepines and antidepressants will be collected as part of the concomitant medication inquiry.
[10] The mobile nurse will complete the collection of safety laboratory tests, measurement of ECGs, and vital signs at home (and/or applicable location).
[11] Vital signs measurements include HR, BP, and weight.

[12] ECGs will be performed every 6 months unless a safety signal is detected. If a safety signal is detected, the mobile nurse will measure ECGs every 3 months. An ECG safety signal is defined as a QTcF ≥480 ms and ≤500 ms (≥60 ms increase from VTV).
[13] Urine pregnancy tests are to be performed as applicable based on gender and menopausal status. Serum pregnancy tests must be used to confirm a positive urine pregnancy test result.
[14] Safety laboratory tests include potassium, magnesium, calcium, and creatinine clearance.
[15] Creatinine clearance will be calculated using the Cockcroft-Gault equation. Patients that de-escalate to half-doses of IMP will have creatinine clearance monitored more frequently than patients at the full dose, as determined by the investigator (or qualified designee).
[16] UHDRS includes Motor Assessment, Cognitive Assessment (Stroop Interference, Verbal Fluency, and Symbol Digit Modalities Test), Behavioral Assessment, Functional Assessment, Independence Scale, Total Functional Capacity, and Summary sections. UHDRS Motor exam will be modified as portions will be considered "unable to rate" (such as rigidity, tandem walking, and retropulsion pull test tasks).
[17] The C-SSRS "Since Last Visit" version will be utilized at all visits. If the patient scores >2 on the C-SSRS for suicidal ideation, the safety TCs should be performed monthly or bi-monthly per investigator (or qualified designee) judgement.
[18] The safety TCs and remote visits will include an abbreviated PBA-s assessment (a subset of PBA-s questions on depressed mood, suicidal ideation, anxiety, irritability, loss of motivation, and obsessive-compulsive behaviors) when the UHDRS is not completed.
[19] Separate Satisfaction Surveys will be administered to patients and investigators (or qualified designees).
[20] Dispensing of IMP after the VTV will occur as direct-to-patient shipments at approximately 13-week intervals.
[21] The mobile nurse will perform IMP accountability at each home visit. IMP (unused and used packaging) will be collected by mobile nurses at each mobile nurse visit and shipped back to the distributor. All unused IMP will be returned.
Abbreviations: AE=adverse event; BP=Blood Pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiograph; EOS=End of study; EOT=End of treatment; ET=Early termination; F/U=Follow-up visit; HR=Heart Rate; PBA-s=Problem Behaviors Assessment–Short Form; QTcF= QT interval corrected for heart rate using Fredericia's formula; RV=Remote visit; TC=Telephone contact; UHDRS=Unified Huntington's Disease Rating Scale; USV=Unscheduled Visit; VTV=Virtual Transition Visit.

1.4 List of Abbreviations

AE	Adverse Event
bid	Twice Daily
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum Concentration
CMSU	Clinical Materials Services Unit
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCC	Clinical Trials Coordination Center
CYP2D6	Cytochrome P450 2D6
D2R	Dopamine D2 Receptor
DSMB	Data Safety Monitoring Board
DSM-IV-TR	Diagnostic and Statistical Manual – Fourth Edition – Text Revision
DTP	Direct-to-patient
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EM	Extensive Metabolizers
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
F/U	Follow-up
GCP	Good Clinical Practice
HART	ACR16C009: A Multi-center, Randomized, Double-blind, Parallel-group Study Comparing Three Doses of ACR16 Versus Placebo for the Symptomatic Treatment of Huntington's Disease. IND: 77,419.
HD	Huntington's Disease
HDPE	High-density Polyethylene
HSG	Huntington Study Group
HTT	Huntingtin Gene
IB	Investigator's Brochure
IC50	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ID	Identification
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
MermaiHD	ACR16C008: A Multi-center, Multi-national, Randomized, Double-blind, Parallel-group Study Comparing ACR16 45 mg Once-daily or Twice-daily Versus Placebo for the Symptomatic Treatment of Huntington's Disease – Randomized Phase. EudraCT: 2007-004988-22.
mMS	Modified Motor Score
mPPT	Modified Physical Performance Test
MTD	Maximal Tolerated Dose
PBA-s	Problem Behaviors Assessment – Short Form
PDF	Portable Document Format
PET	Positron Emission Tomography

PK	Pharmacokinetics
PM	Poor Metabolizers
PRIDE-HD	A Phase 2, Dose-finding, Randomized, Parallel-group, Double-Blind, Placebo-controlled Study, Evaluating the Safety and Efficacy of Pridopidine 45 mg, 67.5 mg, 90 mg, and 112.5 mg Twice-Daily Versus Placebo for Symptomatic Treatment in Patients with Huntington's Disease (TV7820-CNS-20002) EudraCT: 2013-001888-23; IND 77,419
qD	Once Daily
QTcF	QT Interval Corrected for Heart Rate using Fredericia's Formula
REB	Research Ethics Board
RV	Remote Visit
RV1	First remote visit
S1R	Sigma-1 Receptor
SAE	Serious Adverse Event
TC	Telephone Contact
TFC	Total Functional Capacity
UHDRS	Unified Huntington's Disease Rating Scale
UHDRS-TMS	Unified Huntington's Disease Rating Scale-Total Motor Score
UID	Unique Identification
US/USA	United States of America
USV	Unscheduled Visit
VTV	Virtual Transition Visit

2 BACKGROUND AND RATIONALE

2.1 Background

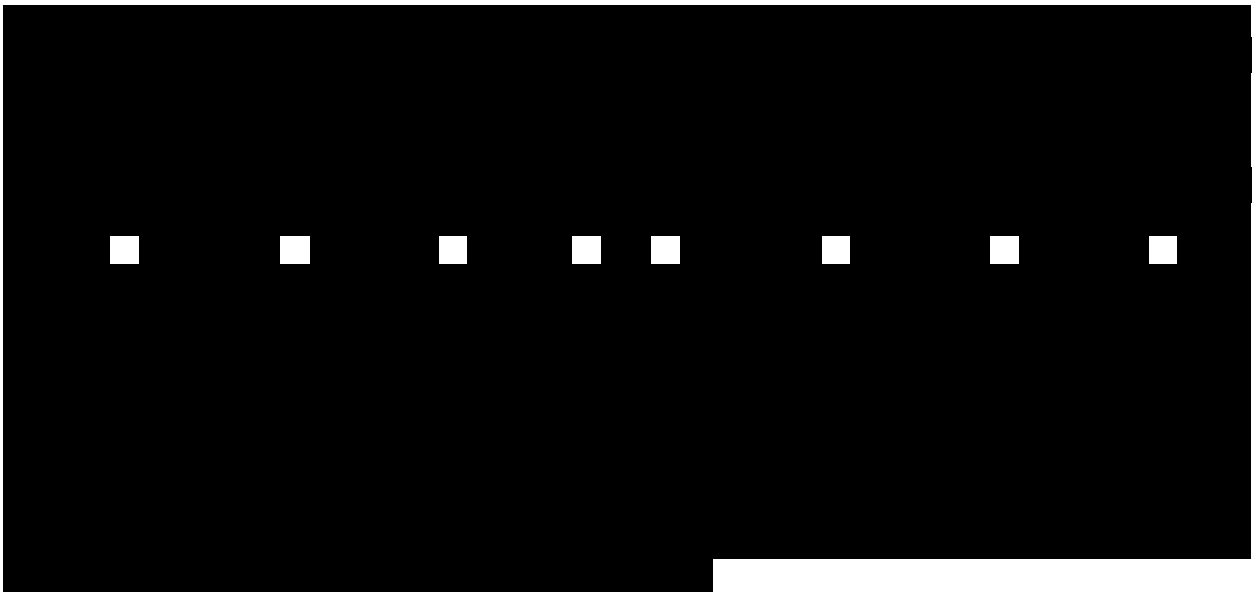
Huntington's disease (HD) is a fatal neurodegenerative disorder with an autosomal dominant mode of inheritance (Quinn and Schrag 1998). HD is caused by a cytosine-adenine-guanine triplet repeat expansion in the huntingtin gene (HTT), which results in an expanded polyglutamine stretch in the HTT protein (Huntington's Disease Collaborative Research Group 1993).

HD is characterized by progressive cognitive decline, psychiatric and behavioral symptoms, and a movement disorder syndrome often including choreiform movements. The age of onset of the signs and symptoms of HD and the rate of disease progression can vary greatly. Adult onset HD most often begins between 30 and 40 years of age. The illness generally lasts 15 to 20 years and is fatal. Following diagnosis, motor and cognitive functions steadily decline, ultimately leading to a state of immobility, dementia, and premature death (Ross and Tabrizi 2011). Psychiatric and behavioral symptoms often start before the onset of motor symptoms, but may also develop with the progression of disease. Not all individuals with HD experience the same psychiatric symptoms, which commonly include anxiety, depression, obsessive-compulsive behaviors, and personality change. Patients with HD commit suicide 4 to 8 times more often than the general population (Farrer 1986, Schoenfeld et al 1984). All patients with HD also have progressive cognitive impairment that is often characterized by executive dysfunction, especially early in the disease, but other cognitive realms are also affected, including learning and memory, motor planning, processing speed, attention, visuospatial processing, timing, emotion processing, and working memory. Cognitive impairment is a major contributor to disability among patients with HD (Ross et al 2014) and is associated with meaningful decrement in functional capacity, driving proficiency, ability to conduct accustomed work, and quality of life (Paulsen and Long 2014).

Pridopidine (TV-7820; formerly ACR16 and ASP2314) is an investigational, oral small molecule in development for the treatment of HD under investigational new drug (IND) application 077419. Pridopidine has been granted orphan drug designation both in the US (12 December 2005, Orphan Designation No. 05-2139) and the European Union (EU/3/05/288) as a treatment for adults with HD. It was originally described as a dopamine stabilizer, with effects regulating dopamine-dependent behaviors. [redacted] Low affinities of pridopidine were also found for several other central nervous system receptor targets (in addition to the D2R), including serotonin 5-HT1A, 5-HT2A, and 5-HT7, adrenergic alpha-1, alpha-2A, and alpha-2C, dopamine D3, muscarinic M2, and histamine H3 (Studies 942038, 942027, and DPR-2014-055), all in the micromolar range (similar to its affinity towards D2R). However, recent studies show that pridopidine has ~100-fold higher affinity for the sigma-1 receptor (S1R; IC50 ~ 100nM) (Sahlholm et al 2013; DPR-2014-055).

Receptor occupancy for the S1R and D2R has been evaluated using in vivo positron emission tomography (PET) imaging in the rat. The PET imaging confirmed that pridopidine occupies the S1R at low doses (≤15 mg/kg) and the D2R at higher doses (more than

15 mg/kg) (Sahlholm et al 2015). After assessing receptor occupancy using (i) known binding affinities of pridopidine to human and rodent S1R and D2R in vitro, (ii) in vivo PET imaging in rats, and (iii) the extensive pharmacokinetic (PK) profiling of pridopidine in the different species, the clinical dose of 45 mg twice daily (bid) is expected to occupy 60% to 85% of S1R and <30% of the D2R. It is speculated that at the low 45 mg bid dose, pridopidine's effect is mainly mediated by the S1R, while at higher doses a more complex activity of pridopidine is initiated by binding to additional low affinity receptors.



As of January 2017, over 1260 subjects (206 of which were healthy volunteers) have been exposed to various oral daily doses of pridopidine in completed and ongoing clinical studies. The majority of the safety database is composed of the HD patients from the HART, MermaiHD, and PRIDE-HD double-blind, placebo-controlled studies (and their corresponding extensions) who received various doses of pridopidine for varying durations for a total of 958.7 patient years.

An integrated safety analysis of the HART, MermaiHD, and PRIDE-HD studies was performed according to the 7 dose groups (placebo, 10 mg bid, 45 mg once daily (qd), 45 mg bid, 67.5 mg bid, 90 mg bid, and 112.5 mg bid) investigated in these studies. Based on the large safety database, the adverse event (AE) profile of pridopidine 45 mg bid is benign and comparable with placebo.

Thus, the 45 mg bid dose has a favorable safety and tolerability profile compatible with continuing development.

2.2 Rationale for Primary Objective and Study Design

The long-term safety profile of pridopidine is not known. For patients previously having taken part in a clinical study, an open-label observational study is the most appropriate study design.

2.3 Rationale for Dosage Used

Patients entering this study were treated with either 0 (placebo), 10, 22.5 or 45 mg pridopidine bid in the HART study, or 0 (placebo), 45, 67.5, 90, or 112.5 mg pridopidine bid in the PRIDE-HD study.

The proposed dose selected for this study is pridopidine 45 mg bid. The proposed dose has been evaluated in 3 large HD clinical studies (HART, MermaiHD, and PRIDE-HD) as well as 2 open-label extension studies (Open-HART and Open-PRIDE-HD) and has been generally well tolerated. In PRIDE-HD, 45 mg bid was the lowest of 4 doses evaluated. [redacted] Thus, from a benefit-risk perspective, the Sponsor sees no benefit in continuing to explore doses higher than 45 mg bid. [redacted] Thus, the Sponsor sees no therapeutic benefit at exploring doses lower than 45 mg bid.

Both pharmacokinetic data and clear dose-dependent and exposure-dependent QTc findings in PRIDE-HD rule out systematic dosing errors. While the HART and MermaiHD studies had explored the clinical profile of doses up to 45 mg bid, PRIDE-HD was designed to test the high end of exposure on potential clinical benefit (Food and Drug Administration [FDA] Type C meeting; 24 July 2013).

The integrated safety analysis and large safety database from the double-blind, placebo-controlled HART, MermaiHD, and PRIDE-HD studies indicated that the AE profile of pridopidine 45 mg bid is generally well tolerated and comparable with placebo. [redacted]

The integrated analysis of data from the double-blind, placebo-controlled HART, MermaiHD, and PRIDE-HD studies indicated the following:

- [redacted]

3 OBJECTIVES

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

3.1 Primary Objectives

The primary objectives are to assess 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.

3.2 Exploratory Objective

The exploratory objective is to evaluate patient and site staff satisfaction with virtual study visits and remote assessments administered in adult patients with HD.

4 STUDY DESIGN

This is a multi-center, open-label study of pridopidine 45 mg bid for patients who completed the HART or PRIDE-HD studies and who transitioned from the Open-HART pre-virtualization study period.

4.1 Centers

Multiple Huntington Study Group (HSG) sites will take part in the virtual aspect of this ongoing study in the US and Canada.

4.2 Patient and Unique Identification Numbers

Each patient is provided a patient identification number. These numbers are used in consecutive order by the site from the site-specific patient identification list provided to the site by the Clinical Trials Coordination Center (CTCC); this four-digit number will identify patients on all study documents and lab specimens. All PRIDE-HD patients have been provided with a new patient identification (ID) number. Patient ID numbers will be documented in the database for future reference. Each patient has a CTCC Unique ID Number that was issued during the HART (ACR16C009) or PRIDE-HD study (TV7820-CNS-20002). This number will enable the CTCC to track individual patients across multiple studies without storing any personally identifiable information.

4.3 Recruitment

This study is open to all patients who have successfully completed the HART (ACR16C009) or PRIDE-HD (TV7820-CNS-20002) studies and transitioned from the Open-HART pre-virtualization study period. No other patients will be recruited into the study.

4.4 Inclusion Criteria

- Patient is able to and has provided written Informed Consent prior to all study-related procedures.
- [Revision 1] Patient has completed the HART (ACR16C009) or the PRIDE-HD (TV7820-CNS-20002) studies and had remained on IMP during the full on-treatment part of the study (including de-escalated patients) or has transitioned from the Open-HART pre-virtualization study period.
- Patient is willing and able to take oral medication and able to comply with the study specific procedures.
- Patient is not participating in another clinical study of an investigational intervention.

- [New criterion] Patient has a wireless internet connection at home (and/or applicable locations) at the first remote visit.
- [New criterion] Patient has the ability to transition from in-person study visits to virtual study visits. The first remote visit (RV1) will take place within approximately 30 days after the last in-person visit.

4.5 Exclusion Criteria

- [Revision 1] Ongoing treatment with tetrabenazine or deutetrabenazine, seizure threshold lowering medications, or certain antipsychotics and antidepressants (see Protocol Section 5.7 and current Operations Manual for list of disallowed medications).
- [Revision 2] Newly instigated or changed treatment with neuroleptics/anti-psychotics.
- [Revision 3] Use of tricyclic antidepressants or class I & III antiarrhythmics at any time during the study period.
- [Revision 4] Any clinically significant, abnormal laboratory result, including clinically significant hepatic or renal impairment, or any ongoing AE that, in the opinion of the investigator (or qualified designee), affects the patient's suitability for the study or puts the patient at risk if he/she continues in the study.
- [Revision 5] A prolonged QTc interval at the RV1 (defined as a QTcF interval of >450 ms for both males and females using Fredericia's formula) or other clinically significant heart conditions as judged by the investigator (or qualified designee).
- [Revision 6] Severe intercurrent illness that, in the opinion of the investigator (or qualified designee), may put the patient at risk when continuing participation in the study.
- [Revision 7] Alcohol and/or drug abuse as defined by the Diagnostic and Statistical Manual - Fourth Edition - Text Revision criteria for substance abuse – this includes the illicit use of cannabis.
- Patients with AEs of suicidal ideation or attempt at any time in the past or as measured by a suicide ideation score of ≥3 on the Columbia-Suicide Severity Rating Scale (C-SSRS) (who answer "Yes" to questions 3, 4, and 5 in the scale suicidal ideation section), or a score of ≥3 on the Problem Behaviors Assessment – Short Form (PBA-s), or patients who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior), if an attempt or acts were performed at any time in the past, or patients who, in the opinion of the investigator (or qualified designee), present a risk of suicide.
- Patients with a known history of epilepsy or a history of febrile seizure(s) or seizure(s) of unknown cause.
- Females who are pregnant or lactating.
- Females who are of child bearing potential and not taking adequate contraceptive precautions (either oral, barrier, or chemical contraceptives) are excluded from the study. Females of child-bearing potential taking acceptable contraceptive precautions can be included.
- Known allergy to any ingredients of the study medication (Please refer to the Investigator Brochure (IB) for a full ingredient list).
- [Revision 8] Creatinine clearance <60 mL/min at virtual transition visit (VTV), calculated using the Cockcroft-Gault equation: (140-age) x mass (kg) x [0.85 if female]/72 x serum creatinine (mg/dL). It is allowed to repeat the test once, if clinically appropriate.

4.6 Conduct of the Study

The ACR16C015 (Open-HART) open-label extension study began in 2011 and has been ongoing in the United States and Canada (see Appendix 1) to evaluate the long-term safety and tolerability of pridopidine administered at a dose of 45 mg bid in adult patients with HD

who completed the treatment period of the HART or PRIDE-HD studies. The primary reason for this amendment is to evaluate the feasibility of virtual study conduct and remote assessments administered in adult patients with HD receiving pridopidine 45 mg bid. All clinical sites will conduct study assessments remotely. The study will consist of a VTV, an open-label treatment period, and a follow-up period (30 days after end of treatment). The study will continue under the same study number; however, all patients will have to be re-consented regardless of their current study status. A CRO will provide oversight and many functions will be performed centrally. The study will include both remote visits and safety telephone contacts (TC). Remote visits will be considered "virtual" visits and will be conducted by investigators (or qualified designees) via real-time video conferencing. Other procedures will be performed by qualified nurses who will visit the patients' homes (and/or applicable locations).

If patients have concerns about the virtual nature of the site visits, they may request an unscheduled visit (USV) at the investigational center. The medical monitor will review individual requests and may approve 1 site USV per patient, per year. The assessments at site USVs will mirror those obtained during safety evaluation TCs (see Section 4.6.4). The investigator (or qualified designee) may schedule additional site visits on a case-by-case basis for patients that require closer monitoring due to safety events.

Patients excluded from the study due to lack of internet connection or inability to transition from in-person study visits to virtual study visits may be eligible to enroll in the Open-PRIDE-HD study (Study TV7820-CNS-20016).

4.6.1 Virtual Transition Visit

The signing of an informed consent form (ICF) and the VTV will be held at the time of the patient's last in-person Open-HART study visit and within 30 days prior to the RV1. Patients may not transition from in-person visits to remote visits before signing informed consent.

After signing informed consent and confirmation of the ability to perform virtual study visits, patients will transition from in-person study visits to remote visits in the Open-HART study.

During the VTV the patient will be asked to appoint a research proxy (see Section 9.2)

IMP will be dispensed at the VTV. All subsequent IMP dispensation will be shipped directly to the patient.

Investigators (or qualified designees) will be trained on video conferencing equipment and remote connection techniques for administration of assessments prior to the patient's first test connection. Patients will be provided with a tablet for remote video conferencing visits after they have completed their last in-person visit and provided written informed consent. A test connection will be completed at the patient's home (and/or applicable location) by the vendor prior to the RV1 to ensure that the investigational site and patient video conferencing equipment are working properly.

4.6.2 First Remote Visit

The RV1 is to be completed within 30 days of the VTV. This visit will be the first virtual visit of the study and will be completed via remote video conferencing. Safety and tolerability will be assessed at all visits of treatment until the end of patient participation, including the follow-up and End-of-Study (EOS) visits. Assessments will be performed according to Section 1.3.

4.6.3 Remote Video and Mobile Nurse Visits

Additional remote video visits will be performed at Weeks 26, 52, and every 26 weeks thereafter (as well as for USVs) until study discontinuation. During these virtual visits, inquiries about AEs, concomitant medication (including changes in use of benzodiazepines and antidepressants), changes in use of alcohol and drugs associated with substance abuse (legal or illicit); an evaluation for research study consent; C-SSRS collection; abbreviated PBA-s collection (a subset of PBA-s questions on depressed mood, suicidal ideation, anxiety, irritability, loss of motivation, and obsessive-compulsive behaviors); and the UHDRS will be conducted by the investigator (or qualified designee). The UHDRS will only be collected at remote visits every 52 weeks and at EOS/ET or USVs. The abbreviated PBA-s will be collected at visits when the UHDRS (Behavior) is not collected.

Remote video visits will be accompanied by an in-person visit from a mobile nurse (within 7 days). Mobile nurses will perform safety laboratory tests, pregnancy tests, vital sign measurements, ECGs, weight, and IMP accountability at the patient's residence (and/or other applicable location) at the time points listed in Section 1.3.

4.6.4 Safety Evaluation Telephone Contacts

Safety evaluation TCs will be conducted by the investigator (or qualified designee) between remote visits at Weeks 13, 39, 65, 91, and every 13 weeks thereafter as well as at unscheduled visits (USVs). During these TCs, inquiries about AEs, concomitant medication (including changes in the use of benzodiazepines and antidepressants), changes in use of alcohol and drugs associated with substance abuse (legal or illicit), an evaluation for research study consent, C-SSRS collection, and abbreviated PBA-s collection will be conducted by the investigator (or qualified designee). The investigator (or qualified designee) will also discuss IMP compliance with the patient during each TC. Assessments will be collected according to Section 1.3.

4.6.5 Unscheduled Visit(s)

USVs may occur as needed and can be completed via remote video, in-person visit, or TC (TC will be the primary form of contact; remote video or in-person visits may be scheduled at the discretion of the investigator [or qualified designee]). The USV may be used to perform assessments per the investigator's (or qualified designee's) judgement. The following assessments are required at an USV: AE review and concomitant medication inquiry. An USV may also be used to re-consent a patient, if necessary.

If patients have concerns about the virtual nature of site visits, he/she may request an USV at the site. The medical monitor will review individual requests and may approve 1 site USV per patient per year. The assessments at site USVs will mirror those obtained during safety evaluation TCs (see Section 4.6.4). The investigator (or qualified designee) may schedule additional site visits on a case-by-case basis for patients that require closer monitoring due to safety events.

If a patient has tolerability problems, or has to de-escalate the investigational medicinal product (IMP), the investigator (or qualified designee) can decide to call the patient to an USV at the investigational center. Patients should be advised that if tolerability problems continue, then they should contact their investigator (or qualified designee) who may then withdraw them from the IMP (see Section 7.7.2).

If a patient attends an USV between the scheduled visits, they should be instructed to attend their next visit according to the study schedule as planned.

4.6.6 End of Treatment Visit

This visit will be completed in place of the Early Termination (ET) visit when a patient is no longer able to receive IMP for various reasons but wishes to remain in the study. Patients who discontinue IMP due to safety or tolerability reasons, or the inability to complete virtual visits, may remain enrolled in the study without treatment at the discretion of the investigator (or qualified designee). Patients should complete the end-of-treatment (EOT) visit and continue with scheduled visits and assessments until the end of study (EOS) or ET. For subsequent visits, these patients will follow the Schedule of Assessments for the remaining remote video/mobile nurse and safety evaluation TC visits.

4.6.7 End of Study/Early Termination Visit

Patients who complete all scheduled visits (remote video and TC) will have procedures and assessments performed via remote video conference and mobile nurse visit at the EOS/ET visit. Patients who withdraw from the study before completing the treatment period will have the EOS visit (or ET) procedures and assessments performed at his/her final visit.

The end of study is defined as the last visit of the last patient.

4.6.8 Follow-up

All patients will be followed for safety via TCs.

4.6.9 Withdrawal From Treatment

If the patient wishes to stop treatment, is judged by the investigator (or qualified designee) to not be suitable for continued therapy, or the study is discontinued, a remote visit ("withdrawal visit", ET visit) should be performed and the patient withdrawn from the study. A (telephone) follow-up visit (30 d TC follow up) to collect and report AEs, concomitant medications (as well as inquiry about changes in use of benzodiazepines and antidepressants), changes in use of alcohol and drugs associated with substance abuse (legal or illicit), C-SSRS, and an abbreviated PBA-s assessment should take place 1 month after the actual discontinuation of IMP took place.

Additional criteria for discontinuation of IMP for individual patients are detailed in Section 7.7.1.

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

4.6.10 Study Duration

The study will continue until:

- the IMP has been authorized for marketing by the respective regulatory authority in Canada or the US; ***or***
- the study is discontinued for medical/scientific (risk-benefit) or commercial reasons.

4.7 Definition of Assessments

4.7.1 UHDRS

Components of the UHDRS (Huntington Study Group, 1996) will be assessed, as detailed below. All UHDRS components will be assessed in-person at the VTV, and some components

will be assessed virtually at the remote visits (RV1, RV3, and RV5) and the EOS/ET and EOT visits, as well as at any USVs, as needed.

4.7.1.1 Motor

The UHDRS motor assessment comprises 31 assessments from the 15 items, with each assessment rated on a 5-point scale from 0 (normal) to 4 (maximally abnormal) (Huntington Study Group, 1996). A modified motor UHDRS will be done, excluding the rigidity, tandem walking, and retropulsion pull test tasks.

4.7.1.2 Function

The functional assessment battery of the UHDRS will be administered. The functional assessment scale assesses 25 items associated with functional problems (Huntington Study Group, 1996).

This scale assesses 5 functional domains associated with disability (occupation, domestic chores, activities of daily living, care level). Individual domain scores range from 2 or 3 (fully functional) to 0 (severely disable), with a total of 13 points possible (Huntington Study Group, 1996).

4.7.1.3 Behavior

This scale measures the frequency and severity of symptoms related to affect, thought content and coping styles. The total behavioral score is the sum of the product (frequency score multiplied by severity score) of all responses. Individual subscales for the various components of the behavioral rating are the product (frequency score multiplied by severity score) for the individual question (Huntington Study Group, 1996).

4.7.1.4 Independence

This is a rating scale where a patient's degree of independence is given in percentage (from 0 to 100%); 100% indicated no special care needed and 0% indicated total care required (Huntington Study Group, 1996).

4.7.1.5 Cognition

The UHDRS Cognitive assessment battery consists of the Stroop Interference Test, Verbal Fluency Examination, and Symbol Digit Modalities Test.

Stroop Interference Test

The Stroop Interference test (Stroop, 1935) measures the ability of the patient to concentrate and ward off distractions. The test consists of 3 items; naming color rectangles (red, green, or blue), reading color words written in black, and naming the color of the ink of incongruent color words. Each test comprises 100 stimuli presented on a card. The test is scored as the number of correct responses made in 45 seconds.

Verbal Fluency Examination

The verbal fluency examination is part of the cognitive assessment battery of the UHDRS. This test constitutes the Controlled Oral Word Association Test (Benton et al 1976). This examination consists of a phonological fluency test. The purpose of the test is to examine the ability of the patient to produce a series of words in response to their phonological characteristics, specifically their first letter. The patient is asked to produce as many responses as possible to a specific letter for 60 seconds. The letters will be appropriate for the language used.

Symbol Digit Modalities Test
The symbol digit modalities test is part of the cognitive assessment battery of the UHDRS. This test constitutes a digit symbol test (Smith, 1968). The patient is given a template of symbols corresponding to the digits 1-9. The patient has then 90 seconds to write as many correct responses as possible.

4.7.2 Columbia-Suicide Severity Rating Scale

The C-SSRS is a 2-page questionnaire designed to systematically and prospectively assess and track suicidal AEs (behavior and ideation) throughout clinical studies.

4.7.3 Problem Behaviors Assessment – Short Form

Because of the prominence of psychiatric symptoms in HD, it is recommended that the PBA-s form be used in all HD studies with any need for behavioral assessment as a comprehensive screen for the most common psychiatric symptoms in HD (Craufurd et al 2001; Kingma et al 2008).The PBA-s is a brief semi-structured interview covering the most common behavioral and psychiatric manifestations of HD. The interview is not restricted to a single construct, but rather covers several broad symptom domains relevant to HD, comprising 11 items: low mood, suicidal ideation, anxiety, irritability, anger/aggressive behavior, loss of motivation, perseverative thinking or behavior, obsessive-compulsive behaviors, paranoid thinking, hallucinations, behavior suggestive of disorientation. Each symptom is rated for severity on a 5-point scale according to detailed scoring criteria, which roughly correspond to the following: 0 = "not at all"; 1 = trivial; 2 = mild; 3 = moderate (disrupting everyday activities) and 4 = severe or intolerable. Each symptom is also scored for frequency on a 5-point scale as follows: 0 = symptom absent; 1 = less than once weekly; 2 = at least once a week; 3 = most days (up to and including some part of everyday); and 4 = all day, every day. Severity and frequency scores are multiplied to produce an overall 'PBA score' for each symptom.

Only the abbreviated PBA-s (i.e. items of the PBA-s relevant to suicidality [depressed mood, suicidal ideation, anxiety, irritability, loss of motivation, obsessive-compulsive behaviors]) will be collected during the TCs and virtual visits when the UHDRS is not completed. If the patient has a positive score 1 and 2 on the suicidal ideation item or depressed mood item of the PBA-s, the patient will be monitored more closely and treated according to the investigator's (or qualified designee's) medical judgment. Patients with C-SSRS or PBA-s suicidality scores 1 and 2 may be handled by investigator (or qualified designee)/neurologist with a consultancy with psychiatrist(s) where necessary per investigator's (or qualified designee's) medical judgement.

A referral for psychiatric evaluation is required for AE/serious adverse event (SAE) of suicidal ideation/suicidal attempt or significant increase in the suicidality scale from baseline (e.g. 2 point increase or higher) or C-SSRS (who answer "Yes" to questions 3, 4, and 5 in the scale suicidal ideation section) or PBA-s suicidality score 3 and above. All patients with PBA-s suicidal ideation item score ≥3 (i.e. 3, 4) will be discontinued from treatment with IMP. Patients who are discontinued from IMP may continue their participation in the study and perform the scheduled visits and assessments, while off IMP. They will continue to be closely monitored by the investigator (or qualified designee) and will be referred for psychiatric evaluation per the investigator's (or qualified designee's) medical judgment.

4.8 Protection of Clinical Study Patients

Informed consent will be obtained from each patient prior to initiation of any study activity.

Designation of a research proxy will be provided by the research patient; the research proxy will be involved in the patient's study participation if the investigator (or qualified designee) determines at some point the patient is no longer able to make decisions independently.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Assignment of Treatment

All patients will receive pridopidine (TV-7820, formerly ACR16) 45 mg bid – two active 45 mg capsules taken as two separate doses (90 mg pridopidine per day).

5.2 Products

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

All IMP must be stored in a cool dry place below 25°C. IMP must not be frozen or refrigerated.

It is the responsibility of the investigator (or qualified designee) via the mobile nurse to retrieve all unused and all returned used supplies from the patient and to return the supplies to the distributor.

5.2.1 Study Drug

Company Name:	Pridopidine (TV-7820, formerly ACR16)
Chemical name:	4-[3-(Methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride
Presentation:	White hard gelatin capsules or light pink/white imprinted capsules providing 45 mg pridopidine

5.2.2 Placebo

Not applicable.

5.2.3 Control Medication

Not applicable.

5.3 Dosage and Administration

The dose in this study is 45 mg bid. The IMP should be swallowed whole with water. Sufficient IMP will be provided to allow 100% compliance between visits.

The IMP will be dispensed in-person at the VTV and in DTP shipments at 3-month intervals thereafter. Patients may be offered to take the first dose at the investigational center.

5.3.1 Dose Frequency Reduction

In the event of tolerability problems, patients will be instructed to immediately contact their investigator (or qualified designee) to discuss their AEs. The investigator (or qualified designee) will assess whether or not the AEs could be related to IMP and severe enough to warrant a dose frequency reduction. The patients will be instructed to stop taking 1 of the 2 capsules of their daily dose. Arrangements for an USV at the earliest opportunity will be made (see Section 4.6.5). At this visit patients will be provided with instructions regarding the de-escalated dose frequency. Alternatively, patients may be temporarily off drug up to 60 days per year in the event of tolerability problems, as judged by the investigator (or qualified designee).

IMP re-introduction or dose frequency increase back to the previous dose frequency may be considered if the clinical monitor, investigator (or qualified designee), and the patient agree that this should be attempted. Alternatively, qd dosing may be maintained.

Patients should be advised that if tolerability problems continue then they should contact their investigator (or qualified designee) who may then withdraw them from IMP (see Section 7.7.2 for withdrawal procedures).

IMP must be reduced to 45 mg qd for the following events:
- Any QTcF increase >60 ms from the first remote visit
- QTcF ≥480 ms and ≤500 ms
- Creatinine clearance <60 mL/min and >40 mL/min

If an IMP must be reduced to 45 mg qd and the patient is not currently at a study visit arrangements for an USV at the earliest opportunity will be made (see Section 4.6.5). At this visit, patients will be provided with instructions regarding the de-escalated dose frequency.

5.3.2 Investigational Medicinal Product

Capsules will be swallowed whole with water. One capsule should be taken early in the morning and one in the afternoon 7 to 10 hours after the morning dose, irrespective of food.

5.3.3 Placebo/Control Medication

Not applicable.

5.4 Presentation and Packaging

Teva will provide the IMP. The primary packaging of the 30- and 60-count bottles will be done at [redacted] and the secondary packaging and labeling of the IMP will be contracted to [redacted]

An interactive response technology (IRT) system will be used to manage the inventory and distribution of IMP to patients, track IMP, and manage the returns and destruction of the product at the conclusion of the study. At the VTV, patients will receive a 6-month supply of IMP. After the VTV, 3-month supplies of IMP will be distributed directly to the patient via DTP shipments.

The IMP will be packed in high-density polyethylene bottles of 30 or 60 capsules per bottle. Four 30-count bottles will be packaged in a patient specific box (for 60-count bottles, kits will contain 4 bottles). Kits will be provided for each patient according to the dosing schedule at the VTV and at 3-month intervals thereafter. Each box for DTP shipping is good for approximately 3 months of dosing. Patient will take home 4 kits at the VTV, and subsequent kits will be shipped directly to the patient. Patients will be provided with an information sheet. This will include instructions for the patient, in case of tolerability problems, to contact the investigator (or qualified designee) immediately. Separate dosing instructions will be provided for those patients de-escalating their dose frequency.

The label texts will be completed in accordance with the appropriate country regulatory requirements.

5.5 Blinding

Not applicable. This is an open-label study with no blinding.

5.6 Accountability of Investigational Medicinal Product and Patient Compliance

A record will be kept by the IRT system of all IMP shipped to the patient, used, and returned. This record gives details of what IMP each patient received.

All unused IMP and used packaging will be returned by the mobile nurse to the distributor at each visit, and stored until notice of destruction from the Sponsor.

Any re-labeling will be in accordance with the appropriate Good Manufacturing Practices/Good Clinical Practice (GCP) requirements.

The electronic Case Report Form (eCRF) will be used by the mobile nurse to perform IMP accountability during remote visits. Patient compliance will be assessed via inquiry during TCs and by capsule count when the mobile nurse visits the patient. The mobile nurse should count the number of capsules remaining in the treatment packs and discuss with the patient any discrepancies between numbers of capsules taken and numbers which should have been taken since the last visit, and record patient compliance in the eCRF.

5.7 Concomitant Medication

5.7.1 CYP2D6 Substrates With a Narrow Therapeutic Margin

[redacted] in this study, medication containing CYP2D6 substrates with a narrow safety margin, e.g. class I anti-arrhythmics and tricyclic antidepressants, must not be used.

To be eligible for inclusion, patients must not have taken any such drug within 6 weeks of the first remote visit. Patients who are prescribed such medication during the study treatment period must be withdrawn from the study (see Section 7.7.2).

5.7.2 CYP2D6 Inhibitors

[redacted]
The dose chosen in the study is considered safe also for poor CYP2D6 metabolizers. [redacted]. Drugs that are CYP2D6 inhibitors, including paroxetine, are therefore allowed. However, the investigator (or qualified designee) should be aware of the likelihood for a higher exposure in these patients when judging the need for dose de-escalation or withdrawal.

5.7.3 Medication that May Lower the Seizure Threshold

[redacted] medications that lower the seizure threshold must be avoided, and if a patient should start such a medication during the course of the study, he or she must be withdrawn (see Section 7.7.2).

5.7.4 Medication That May Cause QTc Prolongation

In addition to the currently disallowed concomitant medications in the protocol, patients on pridopidine should not be allowed to take the following medications known to have a

substantial increase on QT interval: antidepressants (citalopram and escitalopram); antipsychotics (haloperidol, pimozide, clozapine, sertindole, and ziprasidone); and lithium. If these drugs are required for management of the patient, pridopidine should be discontinued.

5.7.5 General

All medications other than the IMP and disallowed medications (prescriptions or over-the-counter medications) started prior to the study or started during the study, must be documented on the concomitant therapy form in the eCRF.

Patients should continue on any medications which are already being prescribed. As far as possible the doses of these medications should be maintained unchanged throughout the study, unless a clinically-indicated change is needed. New medications may be introduced when judged clinically necessary.

Treatment with any of the disallowed medications listed in the current Operations Manual should not be commenced at any point during the study. If this occurs, the patient must discontinue IMP.

Certain antipsychotic medications (see Protocol Section 5.7 and current Operations Manual for disallowed medications) are allowed.

Where a change in dose of an existing medication or introduction of a new medication, other than excluded medications as above, is unavoidable i.e. where it is essential for the appropriate clinical management of the patient, the patient should wherever possible complete the IMP and all study assessments as per the study protocol.

Any changes to an existing concomitant medication or any new medication started during the study should be recorded in the eCRF.

For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be documented on the AE Form of the eCRF.

As part of the additional implemented monitoring procedures, information regarding changes in use of benzodiazepines and antidepressants will be collected in inquiries about concomitant medication. Inquiries about changes in use of alcohol and drugs associated with substance abuse (legal or illicit) will also be conducted. The information collected as part of the safety monitoring, together with the C-SSRS and the abbreviated PBA-s, will be verified with the patient's caregiver, spouse, or other support person (where necessary)[1].

5.7.6 Other Non-Drug Concomitant Therapy

Other therapy may be administered as considered appropriate by the patient’s physician.

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

5.7.7 Warnings and Precautions

[redacted]

[redacted] patients with a prolonged QTcF interval (defined as a QTcF interval of >450 ms for both males and females), or other clinically significant heart conditions will be excluded from clinical studies.

[redacted].

No patients with epilepsy or a history of seizure(s) of unknown cause should be treated with pridopidine. Patients included in studies should be monitored carefully as to exaggerated central nervous system reactions which may be indicative of a higher likelihood of seizure activity.

[redacted] Patients with significant renal impairment (creatinine clearance <40 mL/min) should not be treated with pridopidine.

[redacted] Medication containing CYP2D6 substrates with a narrow safety margin, e.g. class I anti-arrhythmics and tricyclic antidepressants, must therefore not be used.

Full details of AEs observed in reported clinical studies with the IMP can be found in the current Investigator's Brochure.

5.7.8 Availability of IMP After the Study

The study will continue until the IMP has been authorized for marketing by the respective regulatory authorities, or until the study is discontinued for medical/scientific (risk-benefit) or commercial reasons. No further treatment is planned by the Sponsor after the end of the Open-HART study. Patients are advised to return to their primary physician for additional treatment.

6 STUDY METHODS AND ASSESSMENTS

Full details of the required conduct of the study and the schedule of assessments are provided in Section 1.3.

It is recommended that the same qualified and trained investigator (or qualified designee) performs the neurological assessments, if possible. If the investigator (or qualified designee) cannot perform the assessments at a visit, the substituting investigator (or qualified designee) should be appropriately accredited. Investigators (or qualified designees) were trained in motor rating using the UHDRS and other rating scales during the preceding HART and PRIDE-HD studies.

If necessary, other qualified and trained investigators (or qualified designees) can perform other assessments (e.g. cognitive). The information about all personnel that have direct patient contact and the trainings that each one has received must be clearly identified and appropriate regulatory information must be on file.

Mobile nurses will be trained on the conduct of all study assessments before study virtualization.

After the VTV, in order to ensure timely assessments and compliance with IMP, it is recommended that the maximum period between VTV and each subsequent visit are as follows:

VTV to RV1	30 days from VTV
VTV to TC 1	13 weeks ±14 days from VTV
VTV to Remote Visit 2	26 weeks ±14 days from VTV
VTV Visit to TC 2	39 weeks ±14 days from VTV
VTV Remote Visit 3	52 weeks ±14 days from VTV
VTV to TC 3	65 weeks ±14 days from VTV
VTV to Remote Visit 4	78 weeks ±14 days from VTV
VTV to TC 4	91 weeks ±14 days from VTV; subsequent visits are every 13 weeks ±14 days thereafter (in between remote visits)
VTV to Remote Visit 5	104 weeks ±14 days from VTV; subsequent visits are every 26 weeks ±14 days thereafter

The schedule continues going forward in this manner, with alternating TCs every 3 months and remote visits every 6 months until the patient is withdrawn or the study ends.

6.1 Assessment of Efficacy

May be conducted as decided by Sponsor.

6.2 ECG Assessments

A single resting 12-lead ECG will be performed at VTV and all remote visits by mobile nurses. ECGs will be collected using ECG devices and measures of the cardiac intervals and morphological assessment. Participants have to be resting, in a comfortable supine position and environment, at least 15 minutes before each ECG sampling time point through at least 10 minutes after the collection.

A prolonged QTc interval at the VTV (defined as a QTcF interval of >450 ms for both males and females), or other clinically significant heart conditions as judged by the investigator (or qualified designee) is a violation of exclusion criteria and the patient will not be eligible for participation in the study.

QTcF Formula to be used: $QTcF = QT/\sqrt[3]{RR}$

Any clinically significant abnormalities observed by the investigator (or qualified designee) must be reported as AEs.

In instances where there is an increase in QT/QTcF of >500ms or 60ms over the VTV, a second ECG should be repeated after 10 minutes rest to confirm the finding. Where confirmed, this should be reported and documented on the eCRF as an AE.

Patients with a QTcF interval of >500 ms or if an increase in the average QTcF value is >60 ms from the VTV should be discontinued from the IMP and may remain in the study off IMP. A follow-up ECG should be done in 4 weeks.

If the central ECG reading results match the above criterion, the patient should stop taking IMP and may remain in the study off IMP.

6.3 Laboratory Assessments

6.3.1 Collection of Blood Samples

Additional blood samples may be done at the discretion of the investigator (or qualified designee), if (for example) an AE is suspected (see Section 7).

6.3.2 Laboratory Results Outside the Normal Range

All laboratory values that fall outside the reference range and are of potential clinical relevance should be noted and commented upon by the investigator (or qualified designee). The appearance of abnormal laboratory results or significant shifts from VTV, considered to be clinically significant by the investigator (or qualified designee) are to be documented as an AE (see Section 7.1.1). Any abnormal laboratory results obtained should be considered by the investigator (or qualified designee) as related to previous use of pridopidine in Open-HART, in which case they will be considered treatment-emergent AEs.

Calcium, magnesium, and potassium levels will be drawn every 6 months [hypokalemia is defined as a potassium level of <3.5 mEq/L)]. If <3.5 mEq/L, patient's study drug will be suspended until normal (≥3.5 mEq/L).

If hypokalemia is observed, dosing will be interrupted and should not be started again until normal electrolyte values are confirmed by re-draw and maintained for 7 days. Patients needing more than 14 days to reach stable potassium levels, without IMP, should be withdrawn from IMP. The patient will be asked to continue in the study and follow the visit schedule as outlined in the protocol.

[redacted], and to ensure a reasonable minimum clearance in all patients through the renal pathway, patients with a creatinine clearance <60 mL/min (calculated by the Cockcroft-Gault formula) will be excluded from the study or may be able to take a lower dosage of IMP (45 mg qd) if his/her creatinine clearance is <60 mL/min and >40 mL/min, per discretion of the investigator (or qualified designee). Patients that de-escalate to half-doses of IMP will have creatinine clearance monitored more frequently than patients at the full dose, as determined by the investigator (or qualified designee). Patients will be discontinued from treatment with IMP if their creatinine clearance decreases to <40 mL/min during their participation in the study. The test may be repeated once, if clinically appropriate.

6.3.3 Pregnancy Test

Women of childbearing potential should have a pregnancy test performed and results confirmed before study drug administration at the VTV, RV1, and annually thereafter as well as at EOT, EOS/ET, and USVs, as needed.

6.4 Vital Signs and Physical Examination

Systolic and diastolic blood pressure and heart rate must be measured by mobile nurses at VTV and all remote visits as well as at EOT, EOS/ET, and USVs, as needed. Physical examination will be performed at the VTV only.

6.5 Body Weight

Patients must be weighed lightly clothed by mobile nurses at the VTV and all remote visits as well as at EOT, EOS/ET, and USVs, as needed.

7 SAFETY PARAMETERS AND ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

This definition includes accidental injuries, study drug intolerance, overdosing, reasons for any unplanned change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures. It also includes AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP. In addition, any laboratory abnormality assessed as clinically significant by the investigator (or qualified designee) must be recorded as an AE.

7.1.2 Pre-Treatment Adverse Event

A pre-treatment AE is any untoward medical occurrence arising or observed between informed consent and start of IMP.

7.1.3 Treatment-Emergent Adverse Event

A treatment-emergent AE is any AE occurring after start of IMP and within the time of residual drug effect, or a pre-treatment AE or pre-existing medical condition that worsens in intensity after start of IMP and within the time of residual drug effect.

The time of residual drug effect is the estimated period of time after the last dose of the IMP, where the effect of the product is still considered to be present based on PK, pharmacodynamics, or other IMP characteristics. The time of residual drug effect is for most drugs 5 half-lives of the IMP.

7.1.4 Overdose

A drug overdose is the accidental or intentional use of a drug or medicine in an amount that is higher than the recommended daily dose. In the context of this study, this is defined as any dose above 90 mg pridopidine (TV-7820) daily.

7.2 Collection and Recording of Adverse Events

7.2.1 Collection of Adverse Events

The investigator (or qualified designee) must monitor the condition of the patient throughout the study from the time of obtaining informed consent until the EOS visit or end of follow-up period, as applicable.

AEs include:

- Patients positive response to questions about their health (at each visit, AEs will be elicited using a standard non-leading question such as "How have you been feeling since your last visit?")
- Symptoms spontaneously reported by the patient.
- Clinically relevant changes and abnormalities observed by the investigator (or qualified designee) (e.g. local and systemic tolerability, laboratory measurements, results of physical examinations, etc.).

If a patient suffers from the same AE more than once and the patient recovers in between the events, the AEs should be reported separately.
The investigator (or qualified designee) must record all AEs on the AE Log provided in each patient's eCRF with information about:

- AE
- Date of onset and time of onset
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date of outcome and time of outcome
- Outcome

Each of the items on the AE Log is described in detail in the following sections.

7.2.2 Adverse Event

AEs should be recorded as diagnoses, if available. If not, separate sign(s) and symptom(s) are recorded. Only one diagnosis/symptom should be entered per record.
Pre-existing clinically significant conditions diagnosed or observed as a result of the screening procedures must be recorded as AEs. However, pre-existing, known clinically significant conditions observed at screening should be recorded as medical history.

The following exceptions should be noted when recording AEs:

- Death is not an event but the cause of death is. An exception is the event of sudden death of unknown cause.
- Hospitalization is not an event but the reason for hospitalization is.
- Procedures are not events, the reasons for conducting the procedures are. In general, only the reason for conducting the procedure will be captured as an AE. However, if deemed necessary by the investigator (or qualified designee), a procedure can be captured along with the reason for conducting the procedure. E.g. if the procedure "eye surgery" was performed due to "diabetic retinopathy", "diabetic retinopathy" (the reason) must be recorded as an AE, and if the investigator (or qualified designee) assess it is of importance, "eye surgery" can be entered as an additional AE.

- Overdoses and medication errors with or without clinical consequences should be recorded as AEs. In the presence of clinical consequences these should be reported as "XXXX due to overdose". In the absence of clinical consequences this should be specified (e.g. overdose, no AE observed)
- Pre-planned hospitalization for a pre-existing condition that has been planned prior to the start of the study should not be recorded as an AE.
- Pregnancy

7.2.2.1 Date of Onset/Time of Onset

The date/time of onset of the AE is the day the first signs or symptoms of the event appeared (regardless of seriousness). For abnormal clinically significant laboratory values or an outcome of an examination, the date of onset is the day when the sample was taken or the examination performed. For pre-existing clinically significant conditions diagnosed or observed as a result of the screening procedures, the date of onset is the date of the procedure/observation. If an exact date is not available, the best possible estimate should be reported (e.g. in mid-January, 3 weeks ago, etc.).

7.2.2.2 Intensity

The following 3-point rating scale must be used for rating of the intensity of each AE:

MILD:	THE EVENT IS EASILY TOLERABLE AND DOES NOT INTERFERE WITH NORMAL DAILY ACTIVITIES.
MODERATE:	THE EVENT IS TOLERABLE AND THE PATIENT IS ABLE TO PERFORM MOST OF THE DAILY ACTIVITIES.
SEVERE:	THE EVENT CAUSES INABILITY TO WORK OR PERFORM DAILY ACTIVITIES.

7.2.2.3 Causal Relationship to the IMP

The reporter must always report his/her evaluation of causal relationship between the event and the suspect drug. The causal relationship to the IMP must be rated using the following 2-point scale:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to AEs, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	An AE may be considered no reasonable possibility if it is clearly due to extraneous causes or when (at least 2 of the following): • it does not follow a reasonable temporal sequence from the administration of the IMP. • it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • it does not follow a known pattern of response to the IMP. • it does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration can neither be ruled out with certainty nor felt with a high	An AE may be considered reasonable possibility related if or when (at least 2 of the following): • it follows a reasonable temporal sequence from administration of the IMP. • it cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or

	degree of certainty to be related to the IMP.	other modes of therapy administered to the patient. • it disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • it follows a known pattern of response to the IMP.

7.2.2.4 Action Taken to IMP

The action taken to the IMP in response to an AE must be classified as one of the following:

- None
- Discontinued
- Temporarily discontinued
- Dose decreased
- Dose increased

7.2.2.5 Other Action Taken

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

All actions taken to treat the event should also be reported. If medication is administered to treat the AE, this medication should be entered in the Concomitant Medication Log (regardless of seriousness).

7.2.2.6 Date of Outcome/Time of Outcome

The date/time of outcome must always be collected when the event has recovered, recovered with sequelae, or the patient died. If an exact date is not available, the best possible estimate should be reported (e.g. in mid-January, 3 weeks ago, etc.).

7.2.2.7 Outcome

The outcome of an AE must be classified as one of the following:

RECOVERED:	THE EVENT HAS FULLY RECOVERED. IF THE EVENT WAS WORSENING OF AN UNDERLYING MEDICAL CONDITION, THE EVENT IS CONSIDERED RECOVERED WHEN THE CONDITION HAS RETURNED TO THE INITIAL LEVEL.
RECOVERED WITH SEQUELAE:	THE EVENT HAS RECOVERED, BUT THE PATIENT HAS DEVELOPED CHRONIC SEQUELAE AS A CONSEQUENCE OF THE EVENT.
NOT YET RECOVERED:	THE EVENT WAS ONGOING AT THE TIME OF THE REPORT.
DEATH:	THE PATIENT DIED.

7.3 Follow-up of Adverse Events

During the study, the investigator (or qualified designee) must follow-up on each AE until it is resolved or until the medical condition of the patient is stable.

After the EOS, the investigator (or qualified designee) must follow-up on any AEs classified as serious or as related to the IMP until they are resolved, or until the medical condition of the patient is stable, or until 30 days (whichever comes first). All such relevant follow-up information must be reported to [redacted] Teva. If the event is a chronic condition the investigator (or qualified designee) and the Sponsor may agree if further follow-up is not required.

7.4 Adverse Events of Special Interest

Seizure/Convulsion

The investigator (or qualified designee) must **immediately** report any case of seizure(s) or convulsion(s) as a medically important SAE. The investigator (or qualified designee) shall report such cases to [redacted] Teva following the procedure and timelines for reporting of SAEs. Any patient that experiences a seizure must be withdrawn from the study.

Pregnancy

The investigator (or qualified designee) must **immediately** report all pregnancies in case any of the study patients or patient's partner becomes pregnant. If a study patient becomes pregnant, the IMP should immediately be stopped and the patient will be withdrawn. Note that pregnancy itself is not an SAE, however, pregnancy should be reported using the Pregnancy Report Form and should be reported within the same timelines as for SAEs.

All pregnancies which are identified during the clinical study must be followed up until delivery and 1 month after delivery or termination. Follow-up should be done using the Pregnancy Report Form.

In case a pregnancy results in an abnormal outcome an SAE Form must be filled in and reported within the timelines stated for SAEs.

Suicidal Ideation or Suicidal Attempt

AEs of suicidal ideation or attempt should be reported to the Sponsor within 24 hours of learning of the event (expedited reporting, regardless of seriousness). The corresponding dedicated eCRF should be completed, but the events should not be marked as serious unless deemed serious by the investigator (or qualified designee). The words "protocol defined AE" should be added after the AE term. Once the AE of suicidal ideation or attempt is received, the patient should be discontinued from the study and from IMP, and referred to a psychiatrist for evaluation and monitoring (see Section 7.7.2).

Standard emergency medical procedures should be followed for any medical and safety concern when immediate intervention is needed (refer to protocol-specific Escalation Plan).

Reportable Events

If a patient stops IMP due to intolerability or an adverse reaction, the site must notify the [redacted] within 72 hours after being informed that treatment was stopped.

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

7.5 Serious Adverse Events

7.5.1 Definitions

7.5.1.1 Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening[2],
- Requires inpatient hospitalization or prolongation of existing hospitalization[3]
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect,
- Other important medically condition[4].

An AE caused by an overdose or medication error is considered serious if a criterion listed in the definition above is fulfilled.

7.5.2 Collection and Recording of Serious Adverse Events

7.5.2.1 Serious Adverse Event Form (SAE Form)

The investigator (or qualified designee) must capture information for each SAE on the SAE Form. The information captured should be the same as described in above sections for AEs. In addition the following information must also be provided:

- Medical history
- Other relevant clinical findings
- Narrative
- Reason for seriousness
- Concomitant medications

All the information provided in the SAE Form **must** match the information captured in the eCRF.

7.5.2.2 Medical History

Relevant updated medical history should be reported with as detailed information as possible including medical term, onset date, and stop date (if not ongoing).

7.5.2.3 Other Relevant Clinical Findings

Other information relevant to the SAE such as hospital records[5], results from investigations e.g. laboratory parameters, invasive procedures, scans and x-rays, and autopsy results should be summarized in the narrative, can be attached to the SAE Form, and must, in any

[2] Life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
[3] Inpatient hospitalization or prolongation should be interpreted as admission for 24 hours or more. Pre-planned hospital admission prior to the start of the study is not considered hospitalization.
[4] Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above should also be considered serious.
[5] Patient details such as name, address, hospital ID number, etc. must always be concealed before sending copies to Teva.

case, be supplied from the investigator (or qualified designee) upon request from the Sponsor. The documents should be provided in English or translated into English.

7.5.2.4 Narrative

The investigator (or qualified designee) must write a narrative of the clinical course leading up to and following the event and provide this narrative in the SAE Form sent to Teva. The narrative should summarise all relevant clinical and related information, including patient characteristics, therapy details, prior medical history, clinical course of the event, and laboratory values. The narrative should be presented in a logical time sequence and give a full overview of the cause of event(s), making the case understandable to persons without existing knowledge of the patient and without access to the patient's hospital records. If laboratory results are presented, reference ranges should be included. If the patient was hospitalized, dates of hospital admission and discharge should be included.

7.5.3 SAE Reporting Responsibilities of the Investigator (or Qualified Designee)

All SAEs must **immediately** be notified to the [redacted] Teva as soon as it becomes known to the investigator (or qualified designee) and not later than within 24 hours of their knowledge of the occurrence of an SAE according to contact details given below. The notification shall at minimum contain investigational site ID, patient ID, AE, investigator causality, and seriousness criterion.

The investigator (or qualified designee) must transmit the completed SAE Form with the fullest possible details to **Teva Pharmaceuticals** by fax or e-mail **within 2 calendar days** of their knowledge of the SAE.

Serious Adverse Event Reporting Contact Information
[redacted]

It is the responsibility of the investigator (or qualified designee) to comply with their local institutional review board (IRB) or research ethics board (REB) regulations regarding the reporting of AEs.

Standard emergency medical procedures should be followed for any medical and safety concern when immediate intervention is needed (refer to protocol-specific Escalation Plan).

7.5.3.1 SAEs Occurring After End-of-Study

If the investigator (or qualified designee) becomes aware of an SAE after the EOS, which he/she assesses to be related to the IMP, the SAE should be reported to Teva. This applies no matter how long after the end of the study the SAE occurred.

7.5.4 Emergency Contact

In case of emergency or and/or where further advice is required regarding the handling of SAEs, the emergency 24 hour contact phone number should be used.

EMERGENCY CONTACT: [redacted]]

Emergency calls will be handled by a fully qualified clinician. A clinician will be available 24 hours a day, 7 days a week on the telephone number above.

7.6 Expedited Reporting by Teva

7.6.1 Responsibilities

Teva is responsible for reporting relevant safety information to all regulatory authorities, investigators (or qualified designees), and central IRBs/ethics committees (ECs).

7.6.2 Expedited Reporting

All AEs that are **serious, unexpected, and considered related to the IMP** judged by either the investigator (or qualified designee) or Teva require expedited reporting.

The expectedness is assessed by Teva according to the (Investigator's Brochure) IB in force at the time of the event.

All available information relevant to the evaluation of the SAE will be reported.

SAEs will be considered reportable regardless of whether or not the IMP was used in accordance with the provisions in the Protocol and/or the IB.

7.6.2.1 Timelines for Expedited Reporting

Fatal or life-threatening serious, unexpected, related cases occurring in clinical studies require very rapid reporting. Regulatory authorities, ECs and investigators (or qualified designees) shall be notified (e.g. by telephone, facsimile transmission, or in writing) as soon as possible but **no later than 7 calendar days** after first knowledge by Teva. This should be followed by a report that must be as complete as possible within 8 additional calendar days.

Serious cases that are unexpected and related and are not fatal or life-threatening, must be submitted as soon as possible but **no later than 15 calendar days** after first knowledge by Teva that the case meets the minimum criteria for expedited reporting.

7.7 Premature Discontinuation of Treatment

If a patient prematurely discontinues treatment the reason for discontinuation should be recorded on the eCRF.

In the event of tolerability problems during the first 4 weeks, patients will be instructed to immediately contact their investigator (or qualified designee) to discuss their AE(s). Patients who experience any intolerable AEs during the first 4 weeks of the study that, in the opinion of the investigator (or qualified designee) could be related to IMP, will attend an EOT visit and discontinue IMP. In the event of tolerability problems during the remainder of the study, please refer to Section 5.3.1.

7.7.1 Cessation of Treatment

A patient will be classified as having ceased treatment when he or she discontinues IMP, prior to the completion of the prescribed course for any of the following reasons:

- AE
- Death
- Lost to follow up
- Patient withdrew consent
- Major protocol violation
- Pregnancy

- Treatment is no longer appropriate
- Termination of study

If hypokalemia is observed, dosing will be interrupted and should not be started again until normal electrolyte values are confirmed by re-draw and maintained for 7 days. Patients needing more than 14 days to reach stable potassium levels, without IMP, should be withdrawn from the IMP. The patient will be asked to continue in the study and follow the visit schedule as outlined in the protocol.

In instances where there is an increase in QT/QTcF of >500ms or 60ms over VTV, a second ECG should be repeated after 10 minutes rest to confirm the finding. Where confirmed, this should be reported and documented on the eCRF as an AE.

Patients with a QTcF interval of >500 ms, or with an increase in the average QTcF value >60 ms from the VTV, should be discontinued from the study. A follow-up ECG should be done in 4 weeks.

Patients should also be discontinued if:

- they experience a seizure or convulsions (regardless of the relationship to treatment);
- their body weight decreases to <50 kg (may be discontinued based on investigator (or qualified designee) or Sponsor discretion);
- and/or if creatinine clearance decreases to <60 mL/min (calculated using the Cockcroft-Gault equation). It is allowed to repeat the test once, if clinically appropriate.
- they experience an AE/SAE of suicide ideation or attempt; or
- they have a C-SSRS suicidal ideation score ≥3 (i.e. who answer "Yes" to questions 3, 4, and 5 in the scale suicidal ideation section); or
- they have a C-SSRS report of suicidal act; or
- they have an abbreviated PBA-s suicidal ideation item score ≥3 (i.e. 3, 4).

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

7.7.2 Withdrawal

Patients have the right to discontinue IMP at any time and for any reason. The investigator (or qualified designee) also has the right to discontinue IMP if he/she feels that treatment is no longer appropriate, if in his/her opinion the patient's clinical condition is worsening or for an AE(s).

A complete evaluation, as detailed in the study protocol for the EOS Visit, should be carried out at the time of discontinuation. The patient will then be withdrawn from the study.

If the reason for premature discontinuation is an AE or an abnormal laboratory test result, the principal specific event or test must be reported on the appropriate section(s) of the eCRF.

All patients for whom an AE of suicidal behavior/ideation was reported at any time during the study should be discontinued from IMP and the need for an evaluation by a psychiatrist should be assessed. Discontinued patients should attend an ET visit remotely to return IMP, perform IMP accountability, and will be asked to complete all protocol required study procedures. AEs of suicidal behavior/ideation should be followed until resolution of the suicidal behavior/ideation.

All patients who are discontinued from the IMP due to active suicidal behavior/ideation should be referred to a psychiatrist and followed by the investigator (or qualified designee) until resolution of the suicidal behavior/ideation.

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

A patient will be considered to have withdrawn from a study in the following circumstances: death, lost to follow-up, if the patient has withdrawn informed consent, or the investigator (or qualified designee) feels that the treatment is no longer appropriate. If withdrawal is due to an SAE the procedure detailed in Section 7.5.3 should be followed.

Patients with a QTcF interval of >500 ms or if an increase in the average QTcF value is >60 ms from the VTV should be discontinued from the study. A follow-up ECG should be done in 4 weeks.

7.8 Replacement Policy for Patients Who Withdraw

There will be no replacement of patients that withdraw from the study. Patients withdrawing will not be replaced.

7.9 Safety Monitoring

The Sponsor is responsible for continuous safety monitoring, including all AEs, monitoring reports, and any other safety-related information.

During the conduct of this study, an Internal Safety Committee reviews accumulating safety data on a quarterly basis (or meet ad-hoc if a safety concern arises, as detailed in the Internal Safety Committee charter), to ensure the continuing safety of the study patients and study conduct issues.

The Internal Safety Committee receives safety data periodically in an unblinded fashion. They have the right to recommend discontinuation of the study for safety reasons.

All Internal Safety Committee sessions are open. The conduct and specific details regarding the Internal Safety Committee sessions are outlined in the Internal Safety Committee charter.

8 STATISTICAL ANALYSIS

8.1 General Statistical Issues

Continuous data will be summarized using descriptive statistics where the following will be reported:

- n (number of observations)
- Number of missing observations
- Mean
- Standard deviation
- Minimum
- Median
- Maximum

Categorical data will generally be presented using count and percentage.
Specifications will be detailed in the statistical analysis plan.

8.2 Data Sets

The analysis set for safety analysis is defined as all patients who were enrolled in the HART or PRIDE-HD studies and who received IMP, or who continued treatment in the Open-HART study.

The analysis set for efficacy analysis is defined as all patients who were enrolled in the HART or PRIDE-HD studies or continued treatment in the Open-HART study and for whom there is at least one post-virtualization visit with efficacy data.

8.3 Missing Values

Missing values will not be imputed.

8.4 Sample Size and Power Considerations

As this is an open-label extension study, no sample size calculations have been performed.

8.5 Disposition of Patients

The number of patients who entered the study, who completed, and who discontinued prematurely will be tabulated.

Discontinuation will also be summarized by appropriate intervals (every 6 months).

8.6 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be tabulated.

8.7 Concomitant Medication During the Study

Concomitant medication during the study will be listed.

8.8 Efficacy Set

Descriptive statistics of each of the efficacy variables for the efficacy analysis set will be presented by yearly intervals. Changes in efficacy parameters will be calculated both from baseline (in main study) and from start of this extension part.

The efficacy parameters will also be presented graphically.

Efficacy data will be presented for all patients combined.

8.9 Assessments and Analysis of Safety and Tolerability

8.9.1 Exposure

The overall exposure in terms of patient-years will be presented by treatment. The number of patients who had a dosage reduction and who had a suspension of IMP will be presented.

8.9.2 Adverse Events

All AEs starting either after the first dose and until 2 weeks after the last dose (scheduled follow-up period) in Open-HART, or Open-PRIDE-HD and continuing in the virtualized Open-HART or starting after the first dose in the Open-HART virtualization will be reported and regarded as treatment-emergent.

Separate displays will be presented for events starting in the Open-HART virtualization. In these displays, only an overall pridopidine treatment group will be presented. Both crude incidences and incidence rates (patients with events per exposure) will be presented.

Combined AEs from HART and Open-HART (ACR16C009 and ACR16C015, respectively) will be reported through an Integrated Summary of Safety.

The following displays will be generated:

- A brief summary of AEs will be tabulated.
- AEs will be summarized by system organ class and preferred term, severity, and relationship to IMP.
- Separate displays of SAEs and AEs leading to discontinuation will be produced.
- All AEs will be listed.

8.9.3 Other Safety Parameters

Changes in other safety parameters (e.g. QTcF, vital signs, and body weight) will be presented by yearly intervals overall.

9 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the current FDA and International Council of Harmonisation - Good Clinical Practice (ICH-GCP) guidelines and applicable regulatory requirements. ICH-GCP is the international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of patients. The investigator (or qualified designee) will ensure that this study is conducted in full conformance with ethical principles which have their origin in the Declaration of Helsinki, or with the laws and regulations of the country in which the research is conducted, whichever affords greater protection to the individual.

9.1 Indemnity, Insurance, and Compensation

[redacted]

9.2 Informed Consent

Written informed consent in compliance with FDA/competent authority regulations and ICH-GCP guidelines shall be obtained from each patient prior to entering the study.

If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the [redacted] and/or the Sponsor, if appropriate, prior to IRB/REB submission. Once reviewed, the Informed Consent Form (ICF) will be submitted by the investigator (or qualified designee) to his/her IRB/REB (or to the central IRB by the Contract Research Organization [CRO]) for review and approval and to the insurance broker contracted by Teva.

An IRB/REB–approved ICF, providing a written summary of all relevant information, will be given to the patient prior to written informed consent being obtained. Informed consent can only be obtained after a full explanation of the aims, methods, anticipated benefits, and all potential hazards of the study have been given to the patient by the investigator (or qualified designee) and when the investigator (or qualified designee) is assured that the patient fully understands the implications of participating in the study.

At all centers the ICF will be signed and dated by the patient and the investigator (or qualified designee). The investigator (or qualified designee) must store the original signed ICF. A copy should be given to the patient.

If the ICF is revised during the course of the study, all active participating patients must sign the revised ICF.

It is recognized that patients enrolled in OPEN-HART may experience progressive cognitive impairment, potentially involving loss of capacity to provide continued consent throughout the study. To ensure ongoing enrollment is appropriate under these circumstances, patients will appoint a research proxy.

During the VTV, the patient will be asked to identify their research proxy. At this visit, patients will provide written consent to allow their research proxy involvement in decisions regarding study participation if the investigator (or qualified designee) determines at some point the patient is no longer able to make decisions independently. In advance of this visit, patients will be encouraged to thoroughly discuss and document their future study participation wishes with the designated research proxy before reviewing their preferences with the investigator (or qualified designee).

Throughout the study, the investigator (or qualified designee) will be responsible for regularly determining the patient's mental capacity and considering if the research proxy should be contacted to discuss the risks and benefits of continued enrollment. The research proxy will be contacted by telephone during study visits, if he/she is not already present, if the investigator (or qualified designee) determines that this is needed.

At follow-up visits for patients who lose capacity to provide ongoing consent, study staff who are qualified to obtain consent will document lost capacity. Discussions with the patient's designated research proxy at each visit and notation of the patient's completion of a research proxy form will also be documented.

On a state-by-state/provincial basis, the accepted term for the designated research proxy may vary, as will the specific consent format, but the specific objective of this plan is for the investigator (or qualified designee) to 1) continually assess the patient's capacity to make

decisions and 2) ensure the patient's wishes with respect to participation in the study are respected.

9.3 Approvals

9.3.1 Institutional Review Board/Research Ethics Boards Approval

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/REB prior to participation of human patients in research studies. The protocol, ICF, advertisements to be used for patient recruitment and any other written information regarding this study to be provided to the patient must be approved by the IRB/REB prior to commencement of the study. Documentation of all IRB/REB approvals and of the IRB/REB compliance with ICH Guideline E6 will be maintained by the center (a copy will be provided to the [redacted] and will be available for review by the Sponsor or its designee.

All IRB/REB approvals should be signed by the IRB/REB Chairman or designee and must identify the IRB/REB name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted.

Where an investigator (or qualified designee) or other staff member is a serving member of the Ethics Committee, he should take no part in the protocol approval process other than to provide additional information to the committee, if requested.

The investigator (or qualified designee) is responsible for obtaining continued review of the research at intervals on an annual basis or otherwise specified by the IRB/REB. The investigator (or qualified designee) must supply the [redacted] and the Sponsor with written documentation of continued review of the clinical research. For sites using the central IRB, the CRO will complete continuing review submissions at intervals specified by the central IRB. The CRO must supply [redacted] and the Sponsor with written documentation of the continued review of the clinical research.

The IRB/REB will be notified by the investigator (or qualified designee) within 90 days the end of the clinical study (last patient, last visit). The investigator (or qualified designee) will also inform the IRB/REB within 15 days should the study be terminated early and the reasons why.

9.3.2 Regulatory Approval

Teva will be responsible for ensuring that the relevant regulatory approval (US IND/Canadian CTA) is obtained prior to study start. Documentation regarding regulatory approval will be provided to the investigator (or qualified designee).

Teva will forward any protocol amendments to regulatory authorities and will ensure that progress reports and details of any serious protocol violations are provided as required by each regulatory authority.

The regulatory authorities will be informed should the study be terminated early.

The regulatory authorities will be notified within 90 days of the end of the clinical study (last patient, last visit). The FDA/Health Canada will also be informed within 15 days should the study be terminated early and the reasons why.

9.3.3 Protocol Amendments

The investigator (or qualified designee) should not implement any deviation from, or changes to, the protocol without agreement by Teva and the investigator (or qualified designee) and prior review and documented favorable opinion from the IRB/REB and FDA/Health Canada, if required, except where necessary to eliminate an immediate hazard(s) to the study patients.

Urgent Amendments
A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided FDA/Health Canada and the reviewing IRB/REB is notified in accordance with applicable regulations.

Amendments Requiring Notification to the FDA
Any changes to the protocol that significantly affects the safety of patients, the scope of the investigation or the scientific quality of the study must be notified to the FDA and the IRB responsible for the review and approval of the study. The amendment(s) should then be forwarded to the FDA and IRB in accordance with FDA 21 CFR (Code of Federal Regulation) Part 312.30 (Protocol Amendments).

Changes to the protocol which meet the above criteria may be implemented provided 2 conditions are met:

(a) Teva has submitted the change to FDA for its review; and
(b) The change has been approved by the IRB with responsibility for review and approval of the study.

Teva may comply with these 2 conditions in either order.

A protocol amendment must be submitted to the FDA when a new investigator is to be added to the protocol. Teva shall notify the FDA of the new investigator(s) within 30 days of the investigator being added.

Amendments Requiring Approval of Health Canada
The following amendments to the protocol must be notified to Health Canada:

(a) affecting the selection, the criteria for selection, monitoring, or dismissal of a clinical study patient;
(b) affecting the evaluation of the clinical efficacy of the IMP;
(c) altering the risk to health of a clinical study patient;
(d) affecting the safety evaluation of the IMP; or
(e) extending the duration of the clinical study.

The protocol amendment may not be implemented until approved by Health Canada.

Teva and the investigator (or qualified designee) reserve the right to terminate the study at any time for safety, clinical, and/or ethical reasons. The procedures for termination will be arranged after review and consultation by both parties. In the case of early termination the Sponsor will notify the competent authority(ies) concerned within 15 days.

9.4 Study Documentation and Study Confidentiality

9.4.1 eCRF and Data Collection

The investigator (or qualified designee) must generate and maintain adequate records (patient medical records, eCRFs, e-source documents) to enable the conduct of this study to be fully documented.

It is the investigator's (or qualified designee's) responsibility to ensure that entries are proper and complete. Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality control, will comply with international regulatory guidelines, including ICH-GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality control, will be described in a data management plan and/or equivalent document.

At the conclusion of the study, the site will be provided with a portable document format (pdf) file on electronic media depicting eCRFs for their site.

Teva's policy is that study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and patients' records (as applicable). The investigator (or qualified designee) must therefore agree to allow direct access to patients' records, and source data must be made available for all study data. The patients must also allow access to the patients' research records, and they will be informed of this and will be confirming their agreement when giving informed consent. The only exception is when study data is recorded directly into the eCRF.

The patients participating in the study will not be identified by name on any study documents to be collected by the Sponsor (or designee), but will be identified by their patient ID Number and initials.

The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the company and investigational staff and are accessible for verification by the study monitor. If electronic records are maintained, the method of verification must be discussed with the investigational staff.

9.4.2 Data Management

Data for this study will be managed using the clinical database management system from Medidata. This is an internet accessible electronic data capture (EDC) application. The EDC application is designed to ensure timeliness and accuracy of data, as well as the prompt reporting of data from the study on an ongoing basis to the investigator (or qualified designee) and to the clinical monitor. The application is compliant with relevant US FDA regulatory requirements including 21 CFR Part 11.

Sponsor will have overall responsibility for the data.

Creation of the analytical database will be covered in the statistical analysis plan.

The investigator (or qualified designee) must be aware of his responsibility to retain patient identification codes in line with regulatory requirements after completion or discontinuation of the study.

If a patient ceases treatment prematurely, then the reason must be noted in the eCRF. If a patient ceases treatment because of an AE, reasonable efforts must be made to clearly document the outcome.

The investigator (or qualified designee) will allow authorized Sponsor personnel, auditors, and regulatory authorities direct access to the patients' research records.

The investigator (or qualified designee) must make study data accessible to the clinical monitor, other authorized representatives of the Sponsor (or designee), and Regulatory Agency (e.g. FDA, Health Canada) inspectors upon request.

Patient identity information will be recorded on the Confidential Patient Identification Code List and maintained for at least 15 years. Research proxy identity information will be recorded on a Confidential Log and maintained for at least 15 years.

Investigators (or qualified designees) must maintain all study documentation for a period of 2 years following the approval date of the drug, or until 2 years after the investigational drug program is discontinued. In the event of an audit or regulatory authority inspection, access to the eCRFs will be provided. Teva will notify the [redacted] and the investigators (or qualified designees) when any records may be discarded.

A record must be kept of all patients who signed consent and were considered for the study and subsequently excluded. The reason for non-participation in the study should be recorded.

9.4.3 Confidentiality of Study Documents and Patient Records

The investigator (or qualified designee) must ensure the patients' anonymity is maintained. Patients must NOT be identified by their name on documents submitted to [redacted]/the Sponsor/third party contractor but by a Patient ID Number and by their initials. The investigator (or qualified designee) will be responsible for maintaining a separate log of patients' codes, names, and unique identifiers. This log will be maintained as required by applicable regulatory requirements. Documents not for submission to [redacted]/the Sponsor/third party contractor, e.g. patients' written consent forms, must be maintained by the investigator (or qualified designee) in strict confidence.

Upon a patient's request and written permission, medical information may be given to his/her personal physician or other appropriate medical personnel responsible for the patient's welfare. The patient and physician must be aware that the information is considered research information.

Data generated for this study must be available for inspection on request to representatives of the FDA, other national or local health authorities, associated IRBs/REBs, the Sponsor and third party contractors.

Additional patient confidentiality issues are covered in the Clinical Study Agreement and in the ICF signed by the patient.

9.4.4 Confidentiality of Proprietary Information

All study related documentation is confidential, whether obtained by the investigator (or qualified designee) or provided by [redacted]/the Sponsor. Disclosure of such information is restricted to those involved in the scientific, ethical, and clinical study procedures.

9.4.5 Financial Disclosure

To meet the requirements of the FDA, all clinical investigators are required to disclose any interests in Teva, the parent company of the Sponsor Company, that they have directly or through close family members. The investigator's disclosable financial interests must be collected during study initiation, following completion of the study at the investigational site, and 1 year following study completion. The investigator should promptly update this information if any relevant changes occur during this period. Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any investigator (or qualified designee) added as investigational staff must complete the Investigator Financial Disclosure Form at the beginning of their participation in the study. For any investigator(s) leaving the site before study completion, an Investigator Financial Disclosure Form should be obtained at the end of their participation.

10 PUBLICATION OF DATA

10.1 Publication

Teva acknowledges that the community of investigators is dedicated to free scholarly exchange and to public dissemination of the results of its scholarly activities. Therefore, the community of investigators or delegated individual investigators shall have the right to publish, either orally or in writing, results arising from the study. The previously appointed HART publication committee (which includes representatives from the community of investigators, a representative of Teva, and the study statistician) will serve as the publication committee for ACR16C015 as well. The publication committee will write and implement a publication plan for the study. The publication committee will, unless otherwise specified in the agreements with the investigators, set the rules for appointing and appoint the primary authors for the planned articles. The rules for appointing authors shall be in conformity with the contract between the [redacted] and Teva.

The authors shall furnish Teva with a copy of any proposed written publication or all other material for any other presentation at least 30 days prior to the submission for publication or presentation for review and commenting. In the event that the proposed publication or oral presentation contains patentable patient matter or other confidential information that needs protection, the community of investigators or delegated individual investigators shall, upon written request from Teva within the 30-day review period, delay the publication or presentation for up to an additional 60 days (which is a maximum of 90 days from the date of submission to Teva) to allow Teva to file a patent application.

Any Teva required modifications or delay will not result in withholding any study results from academic publication.

Authorship of publications arising from this study should be awarded according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, issued by the International Committee of Medical Journal Editors, and community of investigators or delegated individual investigators agree to allow personnel from Teva to be authors when deemed appropriate by said rules.

The investigators acknowledge that the results of the study have to be reported internally within Teva and submitted to the regulatory authorities and the IRB/REB, irrespective of whether the study was terminated prematurely or completed as planned. The investigators also acknowledge that Teva may use data from this study as part of a drug application and/or as part of meta-analyses.

11 ADMINISTRATIVE PROCEDURES

The study will be carried out in accordance with the study protocol, ICH-GCP guidelines, appropriate FDA-CFRs, and local regulatory requirements.

CROs and/or independent contract personnel may be contracted, subject to approval by Teva, to manage and monitor the study, to provide services for data management and statistical analysis, to provide regulatory advice and services, to handle the reporting of SAEs, to provide services for laboratory analysis, to package and distribute the clinical study supplies, and to provide advice on ICH-GCP and quality, and to audit the investigational centers/contractors involved in the conduct of the study.

A full statistical analysis plan will be written in conjunction with the protocol and finalized before database lock. A statistical report will be produced and a final integrated clinical and statistical report will be written in accordance with ICH-GCP by an appropriately qualified individual.

For the purposes of notification to regulatory authorities and ethics committees the end of the study will be defined as being the date of the last visit of the last patient undergoing the study.

11.1 Quality Assurance

Audits may be undertaken by the Sponsor, an independent auditor, and/or regulatory authority. Audits may take place at a investigational center, at the offices of [redacted] during the study or up to a number of years after study closure.

11.2 Monitoring

This study will be monitored by the Sponsor (or designee) in accordance with current GCP. By signing this protocol, the investigator (or qualified designee) grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct remote and on-site monitoring of all appropriate study documentation and/or direct data entry into the eCRF. In order to assure the accuracy of data collected in the eCRFs, it is mandatory that representatives of the Sponsor or designee have access to original source documents (e.g. patient research records, patient research charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality.

The study monitor will contact and visit the site regularly or remotely and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries as compared to source documents. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries and/or direct data entries on the eCRFs. The investigator (or qualified designee) agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.3 Clinical Study Agreement

Agreed costs for each participating center will be met by the Sponsor. For each center, an agreement will be prepared and signed off by the investigator (or qualified designee)/institution and by the [redacted] before the clinical phase of the study commences.

11.4 Investigator (or Qualified Designee) Responsibilities

The investigator will have overall responsibility for the conduct of the study at his/her center. The investigator may delegate specific duties to appropriately trained qualified members of his/her research team or to other hospital staff e.g. mobile nurses, pharmacy, etc. Any delegation must be clearly documented in a center specific delegation list.

11.5 Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies and/or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to the following:

- suspected contamination
- questionable stability (e.g. color change, flaking, crumbling, etc.)
- defective components
- missing or extra units (e.g. primary container is received at the site with more or less than the designated number of units inside)
- incorrect packaging or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor or both
- device not working correctly or appears defective in some manner

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

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the Sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (e.g. the remainder of the patient's drug supply) should be sent back to the Sponsor for investigative testing whenever possible.

11.5.1 Product Complaint Information Needed from the Investigational Center

In the event that the Product Complaint Form cannot be completed, the investigator (or qualified designee) will obtain the following information, as available:

- investigational center number and investigator (or qualified designee) name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint
- associated SAE Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a complaint must not be delayed because not all the required information can be immediately obtained. Known information must be immediately reported. The

sponsor will collaborate with the investigator (or qualified designee) to obtain any outstanding information.

11.5.2 Handling the IMP at the Investigational Center

The investigator (or qualified designee) is responsible for retaining the product in question in a location separate from the investigator's (or qualified designee's) clinical study supplies. The Sponsor may request that the investigator (or qualified designee) return the product for further evaluation and/or analysis. If this is necessary, the mobile nurse or designee will provide the information needed for returning the IMP.

If it is determined that all of the IMP must be returned, the Sponsor will provide the information needed to handle the return by the mobile nurse.

11.5.3 Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an AE or SAE associated with a product complaint, the protocol should be followed (see Section 11.5.4).

11.5.4 Documenting a Product Complaint

The investigator (or qualified designee) will record a description of the product complaint in the source documentation as well as any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the Sponsor and the investigator (or qualified designee), if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

SIGNATURE SHEET

I agree to the conditions relating to this study as set out in this protocol and fully understand that any changes instituted by me without previous discussion with the Sponsor, constitute a violation of the protocol. I agree to adhere to the protocol in all circumstances other than where necessary to protect the well-being of the patient.

I will ensure that the drugs supplied by the Sponsor will be used only for administration to patients included in this study protocol and for no other purpose.

_____ _____

Responsible Principal Investigator (Print Name)

_____ _____

(Signature) (Date)

DSM-IV TR CRITERIA FOR SUBSTANCE ABUSE

DIAGNOSIS – CRITERIA FOR SUBSTANCE ABUSE

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 1 (or more) of the following, occurring within a 12-month period:

(1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g. repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
(2) recurrent substance use in situations in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance use)
(3) recurrent substance-related legal problems (e.g. arrests for substance-related disorderly conduct)
(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g. arguments with spouse about consequences of intoxication, physical fights)

The symptoms have never met the criteria for Substance Dependence for this class of substance

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