Official Title: An Exploratory Phase II Study to Determine the Tolerability, Safety, and Activity of a Novel Vasopressin 1a Receptor Antagonist (SRX246) in Irritable Subjects with Huntington's Disease (HD)

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PROTOCOL TITLE

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SHORT PROTOCOL TITLE
SRX246: Safety, Tolerability, and Activity in Irritable Subjects with HD (STAIR)

Sponsor
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I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with the ethical principles set forth in the Declaration of Helsinki, the Guideline for Good Clinical Practice (ICH E6), the U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21CFR§50), Institutional Review Boards (21CFR§56) and the requirements for conducting clinical investigations (21CFR§312), and all applicable local, state and federal government regulations and laws.

Sponsor Signature: _____
Neal G. Simon, PhD, CEO, Azevan Pharmaceuticals, Inc.

Protocol Principal Investigator Signature: _____
Michael Brownstein, MD, PhD, Vice President, Drug Development, Azevan Pharmaceuticals, Inc.

CAUTION: Investigational New Drug
Limited by Federal (or United States) Law to Investigational Use

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AZEVAN PHARMACEUTICALS, INC. AND THE NEURONEXT NETWORK. Azevan Pharmaceuticals, Inc. (The Company) is the Sponsor organization for this clinical trial. The Company is conducting the trial through the NeuroNEXT Network under a Cooperative Agreement with the National Institute of Neurological Diseases and Stroke (NINDS). The protocol has been reviewed and approved by the NeuroNEXT Clinical Coordinating Center (CCC) and Data Coordinating Center (DCC), as shown by the signatures below.

NeuroNEXT Principal Investigator Approval:

Signature: _____ Date: 8/9/2016

Name: Steven M. Hersch, MD, PhD

NeuroNEXT Clinical Coordinating Center (CCC) Approval:

Signature: _____ Date: 8/16/16

Name: Merit E. Cudkowicz, MD

NeuroNEXT Data Coordinating Center (DCC) Approval:

Signature: _____ Date: 08/15/16

Name: Christopher F. Coffey, PhD

INVESTIGATOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein.

By signing the protocol, the Investigator agrees to keep all information provided by Azevan Pharmaceuticals, Inc. directly, through the NeuroNEXT Network, or by the NeuroNEXT Network itself in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study documents provided by Azevan Pharmaceuticals, Inc. directly, through the NeuroNEXT Network, or by the NeuroNEXT Network itself will be stored appropriately to ensure their confidentiality. The Investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

_____ _____

Site Principal Investigator Signature **Date**

_____

Print Investigator's Name

TABLE OF CONTENTS

LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

ABC	Aberrant Behavior Checklist
AE	Adverse Event
AIC	Akaike's information criterion
ANOVA	Analysis of variance
AUC	Area under the curve
AVP	Arginine vasopressin
BID	Twice a day
BMI	Body mass index
BOLD	Blood Oxygen Level Dependent
BOV	Between-occasion variability
BP	Blood pressure
BSV	Between-subject variability
CAG	Cytosine/adenine/guanine trinucleotide
CCC	Clinical Coordination Center
CDE	Common Data Elements
CDP	Chlordiazepoxide
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CHDI	Cure Huntington Disease Initiative
CHO	Chinese Hamster ovary
CI	Confidence interval
CIRB	Central Institutional Review Board
CMAI	Cohen-Mansfield Agitation Inventory
Cmax	Maximum concentration
CRF	Case report form
CS	Clinically Significant
CSS	Clinical Study Site
CSS PI	Clinical Study Site PI
CSSRS	Columbia Suicide Severity Rating Scale
CTCC	Clinical Trial Coordinating Center
DCC	Data Coordination Center
DM	Data Management
DNA	Deoxyribonucleic acid (c=complimentary; m=messenger)
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EKG	Electrocardiogram
EPM	Elevated plus maze
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
HD	Huntington's disease
HDSA	Huntington Disease Society of America
HIPAA	Health Insurance Portability and Accountability Act
HSG	Huntington Study Group
HR	Heart rate

ICH	International Conference on Harmonization
ID	Identification
IMM	Independent Medical Monitor
IP	Intraperitoneal
IS	Irritability Scale
kD	Kilo Dalton
LAR	Legally Authorized Representative
LMM	Linear mixed models
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
ML	Maximum likelihood
NCS	Not Clinically Significant
NINDS	National Institute of Neurological Disorders and Stroke
NOAEL	No Adverse Effect Level
NOS	Not otherwise specified
OHRP	Office of Human Research Protection
OT	Orthostatic tachycardia
PBA-s	Problem Behaviors Assessment - short form
PK	Pharmacokinetics
PO	Per os (by mouth)
PPI	Protocol Principal Investigator
PSC	Protocol Steering Committee
RIN	RNA Integrity Number
RNA	Ribonucleic acid
RT	Reverse transcriptase
QoL	Quality of Life
SAD	Single ascending dose
SAE	Serious adverse event
SD	Standard deviation
SGOT	Glutamic-oxaloacetic transferase
SGPT	Glutamic-pyruvate transferase
SOP	Standard operating procedure
$t_{1/2}$	Terminal elimination half-life
TFC	Total functional capacity
UHDRS	Unified Huntington Disease Rating Scale
V1a	Vasopressin 1a
VPC	Visual Predictive Checks
pcVPC	Predicted corrected Visual Predictive Checks

1 STUDY OBJECTIVES

1.1 Primary Objective: tolerability

To assess the tolerability of SRX246 in irritable Subjects with early symptomatic HD over a period of 12 weeks compared to placebo.

1.2 Secondary Objective: safety

To assess the safety of SRX246 in irritable Subjects with early symptomatic HD over a period of 12 weeks compared to placebo.

1.3 Exploratory Objectives

To explore the activity of SRX246 in irritable Subjects with early symptomatic HD over a period of 12 weeks compared to placebo, using measures of irritability and other problem behaviors: Aberrant Behavior Checklist (ABC), Cohen-Mansfield Agitation Inventory (CMAI), Problem Behaviors Assessment - short form (PBA-s), and Irritability Scale (IS).

To explore the use of Clinical Global Impression (CGI), Quality of Life (QoL) and Caregiver Burden questionnaires in irritable Subjects with early symptomatic HD who are given SRX246 over a period of 12 weeks compared to placebo.

To explore the use of an eDiary to prompt Subjects to take study drug, and to assess mood and behavior.

To collect sparse sampling population pharmacokinetic data for SRX246 administered to irritable Subjects with early symptomatic HD.

2 BACKGROUND

2.1 Rationale

Huntington's disease (HD) is an inherited disease that results from expansion of a trinucleotide (CAG, cytosine/adenine/guanine) repeat that encodes a polyglutamine tract in the huntingtin gene. How the protein that results from expression of the mutant gene gradually damages neurons is not fully understood, but over time cellular loss affects voluntary motor control, results in involuntary movements (chorea), and causes cognitive decline. Symptoms typically begin between 35 and 44 years of age, but may occur much earlier or later. Psychiatric symptoms, including irritability, are commonly seen in HD, and are quite distressing for patients and their family members. They have adverse effects on daily life, and often result in early institutionalization. While potential disease modifying therapies are being developed to affect the course of the disease, specific therapies that may not be tightly linked to disease pathophysiology are essential for ameliorating the major symptoms of the disease that cause ongoing distress and morbidity. Note that disease-modifying treatments may slow the progression of HD, but not eliminate the symptoms. In this case, symptomatic treatments will continue to be beneficial to the patients. Examples of significant symptomatic treatments for HD that are unrelated to pathophysiology include tetrabenazine for chorea; neuroleptics for chorea or psychosis; and various classes of antidepressant medications. These therapies take advantage of pharmacology unrelated to mutant huntingtin to modulate symptoms that have an enormous impact on quality of life, as could SRX246.

Irritability in HD can be understood as excessive emotional responsiveness or emotional dyscontrol, analogous in many ways to the motor dyscontrol that is pathognomonic for the disorder. Irritability is experienced as episodic, periodic, or chronic internal feelings of anxiety, impatience, and anger and can be manifest externally by being short tempered, impulsive, impatient, volatile, hostile, abusive, agitated, angry, aggressive, and violent. Internal physiological and mental stresses as well as external stresses typically trigger or exacerbate irritability with the reactions often seeming out of proportion to the stressors. Triggers for irritability may not be evident, making environmental modification and behavioral interventions challenging. Patients with HD commonly have limited awareness of the frequency and magnitude of their irritability, may feel that it is justified by circumstance, or may deny it. Since irritability leads to negative actions, interactions and secondary consequences, it can be self-reinforcing, cause others to modify their behavior to avoid exacerbations, contribute to conflict and isolation, and lead to behavior destructive to the environment, to self, and to others, and thus to social, medical, legal, and law enforcement constraints and complications. Its impact on HD families cannot be overstated, since it terrifies those who are at risk for developing HD and drives away caregivers and potential supporters in the community. Irritability and its consequential behaviors are one of the main contributors to use of highly sedating medications and to institutionalization.

Despite the frequent occurrence and severe consequences of irritability, including anger and aggression in HD, the development of specific therapies for these problems has received little attention to date (Thompson 2012).

A review of the literature shows there have been no placebo controlled, randomized treatment studies for irritability in HD (Groves 2011, van Duijn 2010). Irritability is common in

HD and several medication classes are employed in clinical practice to treat this problem, but only a few small studies exist. Further, these studies are challenging to compare, since varying definitions of irritability and assessment scales were utilized. Among these studies are single reports on the use of an SSRI (Ranen 1996), olanzapine (Squitieri 2001), olanzapine with valproate (Grove 2000), and haloperidol with lithium (Leonard 1975). More recently nabilone, a cannabinoid, has been studied (Curtis 2006). These studies are characterized by low levels of evidence and give little indication of treatment efficacy.

Various assessment tools have been used to measure irritability in HD including the Neuropsychiatric Inventory (NPI), the Unified Huntington Disease Rating Scale, the Irritability Scale (IS), and the Problem Behaviors Assessment-short form (PBA-s), but none is well validated for use in clinical trials of drugs. In fact there have been no blinded treatment studies in HD that have used these as outcome measures. The study we propose to undertake will allow us to evaluate the various rating scales that are available, and to obtain data that can be used to plan future Phase IIb or III clinical trials of drugs that might blunt irritability.

One such drug is SRX246, a first-in-class vasopressin 1a (V1a) receptor antagonist that crosses the blood-brain barrier following oral administration. The molecule exhibits high affinity and high selectivity for its target receptor, has a strong safety profile, is well-tolerated, and has excellent pharmacokinetics. Preclinical pharmacology studies have demonstrated significant CNS effects in models of irritability, including impulsive aggression, depression, and anxiety. In an experimental medicine fMRI study in healthy volunteers, SRX246 treatment significantly attenuated the effect of intranasal AVP in brain circuits known to modulate emotional responses to stimuli that elicit aggression/fear. Together, these findings suggest that SRX246 has potential as a novel therapeutic agent for major neuropsychiatric symptoms seen in HD patients, and we propose to test its tolerability in such patients when it is given orally at doses up to 160 mg twice daily.

2.1.1 Patient population

Approximately 150 HD patients with irritability will be screened to enroll 108 Subjects at about 20 NeuroNEXT sites. NeuroNEXT investigators will be responsible for recruitment and follow-up of Subjects in this trial.

2.1.2 Rationale and potential benefits to patients and/or society

Our primary and secondary goals are to test the tolerability and further examine the safety of SRX246, a candidate treatment for irritability in HD. As noted earlier, irritability is highly prevalent in HD. Reported rates range from 40% to 70% (van Duijn 2007). This variation can be explained by use of different assessments and definitions of irritability (which may also include anger and aggression). In order to design, select endpoints for, and properly power clinical trials of novel treatments for the problem, more information is needed about the scales that are available to measure irritability. One of the goals of our study is to provide such information.

2.1.3 Intervention regimens

Irritable HD patients will be randomized into 3-arms: 120 mg BID of SRX246 (n=36), 160 mg BID of SRX246 (n=36), and placebo controls (n=36). All Subjects randomized into the active arms will enter Baseline treatment and receive 80 mg twice daily for 2 weeks, then escalate to 120 mg twice daily for a total of 4 weeks. Subjects randomized to the 120 mg BID group will

continue to take this dose of SRX246 for an additional 6 weeks. Subjects randomized to the 160 mg BID group will increase to this level for 6 weeks. Subjects randomized to the placebo group will be given the same number and type of capsules to take in order to preserve the blind. Dose escalation will occur (stepwise) if patients have not experienced dose-limiting adverse effects. Subjects unable to tolerate the dose escalations can be reduced to the prior dose. Our experimental medicine study strongly suggested that SRX246 inhibits central V1a receptors at a dose of 120 mg BID. The current trial may allow us to determine whether doses of 120 mg BID and 160 mg BID are well tolerated in a sample of male and female HD patients.

2.1.4 Description and justification of the route of administration, dosage, intervention period

While other routes of administration could potentially be used (e.g., delivery via a patch or nasal aerosol), patients in the US are accustomed to taking drugs orally and compliance should be good. BID dosing was selected because the half-life of SRX246 in the blood is approximately 12 hours, and this dosing schedule should provide blood levels of drug that are both adequate and sustained. As noted above, we have chosen doses that bracket the one that proved active in our earlier experimental medicine study. We feel that this study design allows for a rigorous assessment of safety and tolerability, and this should also give us sufficient time to evaluate the behavioral scales that we want to test.

2.1.5 Need, relevance and priority of the study

Irritability (including anger and aggression) occurs commonly in HD patients, but current treatments for these behaviors are empirical or based on small, unblinded clinical trials. Repurposed antidepressant, anxiolytic, and antipsychotic drugs are the mainstays of therapy. We feel that evaluating the scales that are available for assessing irritability, as well as anger and aggression in HD patients, is an especially compelling feature of the work proposed. Actual comparative data about how these scales perform in a clinical trial will be obtained in our target population. This will help us design and power a future efficacy study. Examining the safety and tolerability of our drug at the same time that we collect information about the scales that might be used in Phase IIb and Phase III trials is efficient in terms of both time and overall cost.

2.2 Supporting Data

In this section, we describe the preclinical pharmacology of SRX246, a Phase 1 Single Ascending Dose (SAD) Clinical Trial in healthy human volunteers, a 14-day Phase I Multiple Ascending Dose (MAD) Clinical Trial in healthy human volunteers, a 13-week toxicology study in rat and dog, and an Experimental Medicine fMRI study in healthy volunteers. We show that SRX246: 1) is efficacious in animal models of aggression, anxiety, fear, and depression-like behavior; 2) is safe and well-tolerated in human Subjects with repeat dosing; 3) has an excellent safety profile in both rat and dog after 13 weeks of administration; 4) enters the brain in humans after oral dosing; and, 5) blocks the effect of exogenous, intranasal vasopressin in regions and circuits implicated in irritability, anger, aggression, and other stress-related affective disorders. We believe that these data, combined with additional published preclinical in vitro and in vivo safety and pharmacology studies (Fabio 2013, Ferris 2008, Guillon 2007, Simon 2008), support testing SRX246 in HD patients.

Pre-clinical and clinical studies leading up to, and supporting the proposed research: Aggression, anxiety, and depression are frequently associated with HD. Numerous studies and prominent reviews have described and characterized changes in AVP signaling in preclinical models of these behaviors and in clinical populations (Coccaro 1998, Fabio 2010, Goekoop 2009, Meynen 2010, Landgraf 2006, Ryckmans 2010, Simon 2002). Treatment with SRX246 (oral or IP injection) or very similar V1a antagonist compounds from Azevan's library significantly reduce behaviors in rodents that are thought to model these symptoms in humans (Fabio 2013, Ferris 2008, Simon 2008). Brief summaries of these studies are provided here. Collectively, they strongly suggest that treatment with a V1a antagonist has the potential to address disorders, especially irritability, anger, and aggression that are frequently seen in HD patients.

Aggression: The resident-intruder model is a standard screening test for effects of CNS-active compounds on aggressive behavior. It is commonly used in drug development. An intruder male is introduced into the home cage of the resident male mouse (or rat). During the 5 minute assessment period, resident males reliably attack intruders in more than 90% of trials in our lab. We have tested two Azevan V1a antagonist compounds in this assay, SRX246 and SRX251. The hypothesis that a centrally active V1a antagonist should reduce aggression is based on the relationship between increased vasopressinergic activity and elevated aggression that has been observed in numerous species, including humans (Simon 2002, Ferris 2008). Method: Ten male residents were treated with SRX246 or SRX251 (5 mg/kg) or vehicle by oral gavage. Results: Given as a single oral dose to adult CF-1 male mice 60 min prior to testing, both SRX246 and SRX251significantly reduced the percentage of resident males that attacked the intruder (Vehicle Control 8/10; SRX246 2/10; SRX251 3/10). The few drug-treated males that did attack intruders exhibited significantly less aggressive behavior (fewer attacks and threats) than vehicle-treated control males did. In a second study, we asked if repeat dose treatment for 8 days with SRX251 would reduce aggression. In this study, intraperitoneal (IP) administration was used (2 mg/kg). The results were essentially identical to those observed with a single dose oral treatment: a significant reduction in the percentage of SRX251-treated males that attacked the intruder and, in those that did attack the intruder, a significantly lower frequency of threats and attacks in comparison to controls.

Depression: Chronic social subjugation is a standard method to produce depression-like physiological and behavioral profiles in animals. Berton et al. (2006) described a rapid subjugation paradigm in mice. Using a highly aggressive mouse that had previously defeated the test mouse, leads to diminished social interaction (the dependent measures were distance traveled and time in the Interaction Zone). A 28-day treatment regimen with fluoxetine, an antidepressant, reversed deficits produced by chronic subordination while chlordiazepoxide (CDP) had no effect, supporting the use of the subordination/social interaction model as a rapid behavioral screen for potential antidepressants. SRX246 (5mg/kg) given IP daily for 28 days was tested in this model for antidepressant activity. Results: SRX246 treatment for 28 days produced significant increases in both the time in the interaction zone and the distance traveled there in the presence of a stressful stimulus. Thus, the drug appears to reset the balance between fear of the highly aggressive mouse and the desire to explore and forage in a novel space. In contrast, treatment with CDP (10 mg/kg) had no effect. These results suggest that daily SRX246 at 5 mg/kg IP has antidepressant activity. Unlike fluoxetine, however, SRX246 causes no decrease in sexual activity in treated animals.

Anxiety: The light:dark shuttle box and the Elevated Plus Maze (EPM) tests are standard assays for anxiety. In the light:dark test, anxiety is reflected in time on the dark side while time on the light side reflects lower anxiety. In the EPM, increased time in the open arms of the maze reflect lower anxiety. SRX246 and related V1a antagonist compounds (e.g., SRX251) were given by IP injection to C57/Bl/6j mice (single doses from 1- 10 mg/kg were tested). Results: Treatment with SRX246 produced dose-dependent increases in time on the light side of the shuttle box and in the open arms of the EPM. Both the 5 and 10 mg/kg doses produced significant effects compared to vehicle. These findings suggest that V1a antagonists have anxiolytic properties.

Western Blot Analysis of V1a Receptor in Post-mortem Human Brain Tissue: The vasopressin 1a receptor is extensively distributed throughout the limbic system and cortex of rodents and rhesus monkey (Ring 2005, Ryckmans 2010, Young 1999). The parallel patterns observed in rodent and rhesus brains hinted that the V1a receptor might have a similar distribution in the human brain, but no group has directly shown that V1a receptors are present in human brain tissue. In this study, we tested post-mortem human brains for the presence of V1a receptor using Western Blot analysis.

Post-mortem human brain regions were provided by Dr. Miklos Palkovits, Semmelweis University, Hungary. The brain samples were homogenized in a Tris-buffered sodium dodecyl sulfate solution, followed by gentle sonication yielding a clear lysate. Brain lysates were electrophoresed on ready-made gels, and the proteins were transferred to nitrocellulose membranes. For immunological detection, a mouse monoclonal anti-human V1a antibody (Abnova) was chosen after a preliminary screening of 5 other commercially available V1a antibodies. The antibody recognized a 46-kD protein in CHO cells transfected with a human V1a receptor cDNA, but not in untransfected CHO cells. A 46-kD protein was also seen in a lysate of human blood platelets, which are known to have V1a receptors.

The same 46-kD V1a receptor band was detected in lysates of the following brain areas: anterior cingulate cortex, caudal cingulate cortex, parietal cortex, insular cortex, medial orbitofrontal cortex, medial and lateral amygdala, mediodorsal thalamic nucleus, nucleus accumbens, supraoptic nucleus, and mamillary body. While some samples of the mediodorsal thalamic nucleus and nucleus accumbens had especially high V1a signal intensities, conclusions about relative regional signals are premature due to sample variation and low sample numbers.

Our Western blot study demonstrated that the V1a receptor protein is expressed in several human brain regions, including those involved in the regulation of social and emotional behaviors. This wide distribution in human brain is consistent with that reported for rhesus monkey (Young 1999). These data indicate that the V1a receptor, the target of SRX246, is present in human brain, but not that it is preserved in the brains of HD patients following degeneration of certain neuronal populations. To determine whether this is the case, we performed a second study. Total RNA was extracted from HD and age/gender matched control cerebral cortical samples using an RNeasy® Lipid Tissue Kit (Qiagen). Genomic DNA was eliminated by treatment with RNase-free DNase (Qiagen). The integrity and quality of RNA was determined using an RNA 6000 NanoChip kit and an Agilent 2100 Bioanalyzer (Agilent Technologies). High quality RNAs with Integrity Numbers (RIN) > 7 were studied, with one exception, an HD sample with a RIN of 6.5. Reverse transcription (RT) was performed (12

control RNAs, 10 HD RNAs) using anti-Script cDNA synthesis kit according to the manufacturer's protocol. Real-time quantitative PCR using a SYBR Green QuantiTect RT-PCR Kit (Qiagen) and a BioRad CFX96 Real time PCR detection system was performed according to the manufacturers' protocols. Samples were loaded in quadruplicate; no-template (negative) controls and no-RT controls were included. The expression levels of V1a mRNA were normalized to β-actin. Data analysis was performed using the CFX Manager™ Software.

V1a receptor mRNA levels in HD and control brains were similar. These results indicate that the target receptor for SRX246 is present HD brains; and that, in fact, its expression level is apparently unaltered. Messenger RNA levels are not always reflected in the amount of protein that is finally produced, so we also used Western blotting to measure receptor protein concentrations. In the areas of brain studied, V1a receptor protein levels were virtually identical in HD and wild type samples (data on file).

Phase I Single Ascending Dose Study (SAD): A double-blind, placebo-controlled, ascending, single-dose safety, tolerability, and pharmacokinetic study of SRX246 in capsules was undertaken in healthy adult volunteers. A total of 49 Subjects were enrolled—37 males and 12 females with a mean age of 43.5 years. The Subjects were representative of different races: Caucasian (7), black/non-Hispanic (23), Hispanic (18), Asian/Pacific Islander (1). A single oral dose of SRX246 was administered to a total of 34 Subjects enrolled in a total of 7 separate cohorts. The dosing cohorts were as follows: 20 mg (5 Subjects), 80 mg (2 consecutive cohorts of 5 Subjects each), 160 mg (5 Subjects), 240 mg (5 Subjects), 320 mg (4 Subjects). There were a total of 15 placebo Subjects spread among all cohorts (2 per cohort except for Cohort 7 in which there were 3). All Subjects completed the study; there were no SAEs, deaths, or discontinuations.

Safety summary: A total of 25 adverse events (AEs) were recorded. Overall, no trend was identified in terms of specific organ system affected with increasing dose. In fact, the placebo Subjects experienced a higher absolute number of AEs than the experimental Subjects except for orthostatic tachycardia (OT), which is discussed below. In Cohort 1 (20 mg) a single AE (mild light headedness) was reported. There were no AEs reported in Cohort 2 (40 mg). In Cohort 3 (80 mg) elevations in heart rate (HR) immediately upon standing were described in 3 patients. At the time these events were observed, some of the HR readings were repeated manually; the elevation in HR could not be confirmed, and the "tachycardia" was not accompanied by any clinical symptoms. Nonetheless, the 80 mg dose was repeated in a new cohort of Subjects prior to dose escalation. In this new group of Subjects, there was no orthostatic tachycardia (OT) and no other AEs.

With post-hoc review, a total of 10 additional OT AEs were documented within Cohorts 1, 2, 6 and 7, and were included in the study database. Upon unblinding the study, OT was the only AE noted where there was a higher overall incidence in the active Subjects than the placebo Subjects. However, no dose response relationship was observed as the dose of SRX246 increased from 20-320 mg. The OT AEs were not accompanied by BP changes, and no clinically significant EKG changes were identified during the study. Finally, no clinical signs/symptoms (e.g., chest pain, shortness of breath) were reported at the time the OT AEs were noted, and the Subjects did not experience any clinical sequelae.

PK Summary: The PK data demonstrate that SRX246 is orally bioavailable, with Mean Cmax and AUC values for plasma SRX246 concentration increasing in a dose-proportional manner as the SRX246 dose increased.

Overall conclusion: SRX246 is orally bioavailable as observed by dose-proportional increases in plasma levels, and is safe and well tolerated at the highest dose studied (320mg). Dose-limiting toxicity was not observed during the study. However, based on attaining adequate exposure levels at the highest dose, a determination was made to discontinue dose escalation and the study.

Phase I Multiple Ascending Dose Study (MAD): The results of the SAD study indicated that it would be safe to undertake a multiple ascending dose (MAD) study of SRX246 capsules in healthy volunteers. The SRX246 doses selected for use in the MAD study were 30, 60, and 120 mg administered q12h (i.e., 60, 120 and 240 mg total daily dose, respectively).

In the MAD study, Subjects were 24 healthy, non-smoking men and women of non-child-bearing potential 18-55 years of age. The doses administered were 0, 30, 60, and 120 mg PO BID (q12h) for 14 days. 6 Subjects were included at each dose level, including placebo. There was no Dose Limiting Toxicity observed, no severe AEs, deaths, or discontinuations due to AEs, and all Adverse Events reported were generally mild with the exception of 2 events of moderate severity (left eye sty, contact dermatitis) in the treatment groups. These were not considered treatment-related. The number of adverse events that were considered to be likely to be related to study medication was similar (approximately 25%) in the placebo, SRX246 30 mg BID, and SRX246 60 mg BID groups, and no Subject-reported adverse events were considered to be likely to be related to treatment in the SRX246 120 BID mg group. There was no evidence of any treatment-related effect on vital signs. Although two adverse events of mild tachycardia were reported each in the placebo, SRX246 30 mg and 60 mg groups, there were none in the SRX246 120 mg group. There were no laboratory findings indicative of an adverse treatment related effect, except mild elevation in SGOT and SGPT in 2/6 Subjects receiving active drug at the 120mg/kg dose and 1/6 receiving placebo. No Subjects had a treatment emergent clinically important change in electrocardiogram or physical examination. Overall, SRX246 was safe and well tolerated at doses from 30mg twice daily to 120 mg twice daily for up to 14 days.

The pharmacokinetic data demonstrated that SRX246 is orally bioavailable, with plasma Cmax and AUC concentration increasing in a greater than dose-proportional manner as dose increased. Median time to Cmax (tmax) was from 1.25-2 hrs with tmax ranging from 0.5-4 hrs. Mean $t_{1/2}$ on Days 1 and 7 ranged from 2.1-4.7 hours with PK sampling obtained from 0-12 hrs after the morning dose. Mean $t_{1/2}$ on Day 14 ranged from 4.72-12.94 hrs as the SRX246 dose increased from 30 mg to 120 mg PO BID (q12 hours) based on PK sampling from 0 to 48 hours following the last morning dose. Mean clearance and volume of distribution values suggest SRX246 undergoes modest to high clearance and is widely distributed in body tissues. Steady-state plasma concentrations were achieved by Day 7 and a moderate amount of plasma SRX246 accumulation occurred on Day 14 compared to Day 1, with mean Ro values ranging from 1.35 to 3.68. After 14 days, Cmax and AUC_{0-12} at the 120mg BID dose were 229 ng/ml and 802 ng*h/ml, respectively, and at the 60mg BID dose Cmax =33ng/ml and AUC_{0-12}=110 ng*h/ml. At the 120mg BID dose on Day 14, the $t_{1/2}$ = 12 hrs and the AUC_{0-12} values provide sufficient range to support Phase II. Since the compound has a high molecular weight, appears to undergo very

little metabolism by human liver cells, and is found in low amounts in the urine (817 ng/ml in patients given 120 mg BID), it is likely to be eliminated into the bile (see Hosey 2014 for supporting information). The p-glycoprotein pump involved is saturated between the 30 mg and 60 mg BID doses.

Modeling the PK of SRX246 at a dose of 160 mg BID. The data used are from AVN007, a 14-day Multiple Ascending Dose Phase I study. Compartmental modeling was conducted first. Following compartmental modeling, non-compartmental modeling was conducted to derive Cmax and AUC for different Subjects at different days administered with different doses. The dose and exposure (AUC and Cmax) relationship was explored with linear and nonlinear regression; the linear regression model provided a better fit after taking into account the fact that SRX246 is a P-gp substrate (see below). Based on the derived dose-exposure relationship, AUC_{0-12} and AUC_{0-24} at steady state were predicted for 160 mg BID.

It should be noted that in AVN007, differences were observed for AUC_{0-12} on Day 7 and Day 14. Therefore, the fitting of the Dose and AUC relationship was conducted without combining the AUC data from the different days. Further, while it initially appeared that a nonlinear relationship was observed in AVN007, there is a need to take into account the fact that SRX246 is a P-gp substrate and that the pump is saturated at a dose of 60 mg BID and above. On this basis, a linear PK relationship should be expected at doses of 60 mg and higher, although in a greater than dose proportional manner.

Table 1 and Figure 1 show the predicted AUC0-12h at 160 mg BID with 90% confidence intervals (CI) on Days 7 and 14. Table 2 and Figure 2 show the predicted AUC0-24h at 160 mg BID with 90% confidence intervals (CI) on Days 7 and 14. Table 3 and Figure 3 show the predicted Cmax values for the 160 mg BID dose on Days 7 and 14.

The mean Cmax that SRX246 might achieve at day 14 when it is given at 160 mg BID (360 ng/ml) is substantially higher than the mean Cmax observed at 120 mg BID (229 ng/ml), but well below the concentration seen in rats and dogs at the NOAEL (see below). It is worth noting that in a study conducted by Covance, brain levels of SRX246 after oral administration for 28 days in rat at 20 mg/kg were 25% of those in blood.

Sparse sampling population PK measurements will be conducted to provide additional information about the behavior of SRX246 in humans.

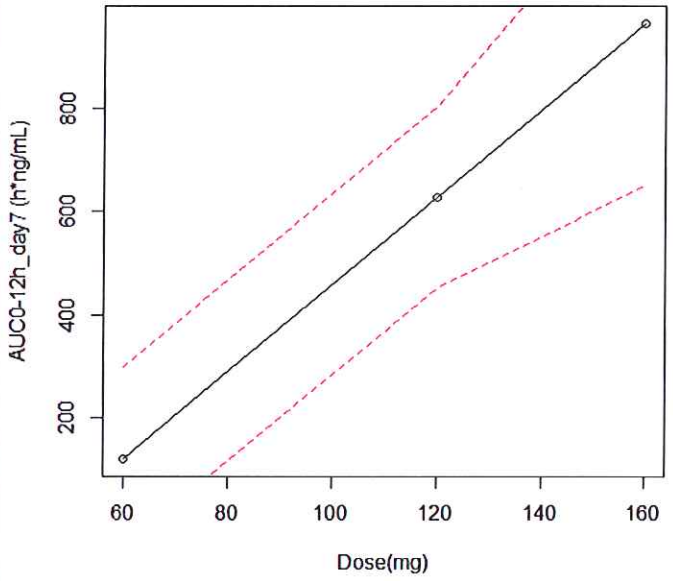
SRX246 is the subject of active INDs #76,142 and #126,047 and the full range of toxicology and safety studies required by the FDA for investigational use in humans have been completed. FDA has affirmed that the 14-day MAD study with SRX246 would be sufficient to support dosing for up to 12 weeks in a Phase II study. A full summary of data is provided in the Investigator's Brochure.

Table 1 Predicted AUC0-12h following multiple doses with 90% CI.

Dose mg BID	Mean	90%CI_Low	90%CI_Upper
Predicted AUC0-12h on Day 7 (ng·hr/mL)			
60	122.1	-53.7	297.8
120	627.1	451.4	802.8
160	963.8	648.3	1279.2
Predicted AUC0-12h on Day 14 (ng·hr/mL)			
60	109.9	-148.2	368.1
120	802.7	544.5	1060.8
160	1264.5	801.1	1727.9

Figure 1 Predicted AUC0-12h following multiple doses with 90%CI

Predicted AUC0-12h on Day 7 with 90%CI



Predicted AUC0-12h on Day 14 with 90%CI

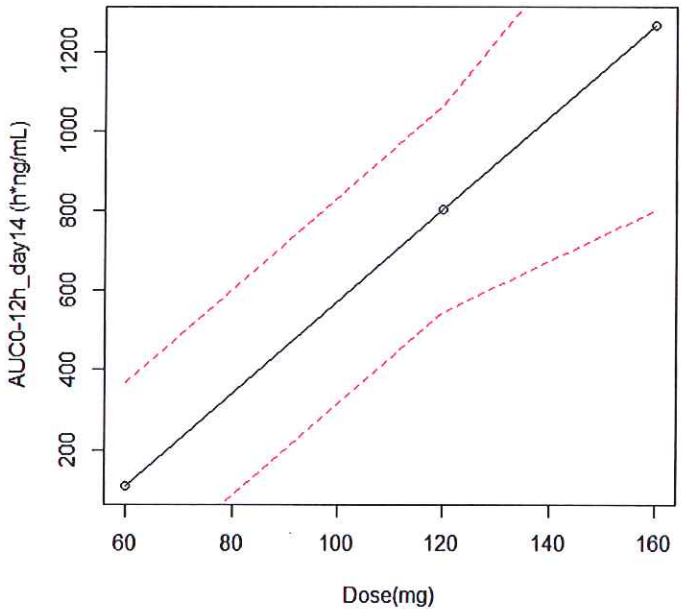
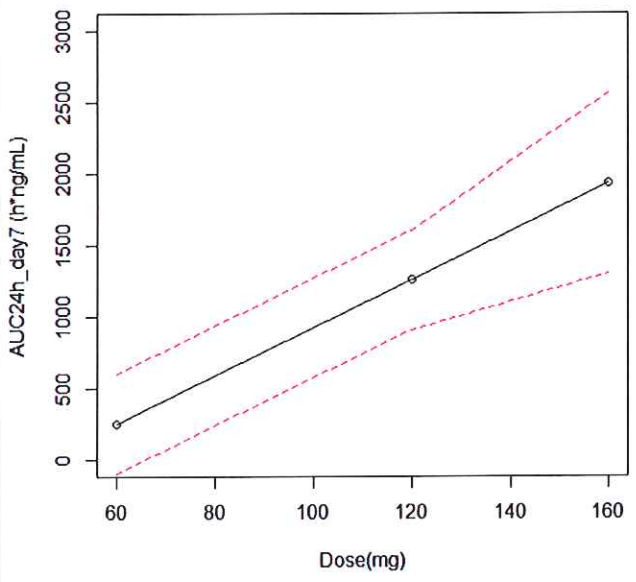


Table 2 Predicted AUC0-24h following multiple doses with 90%CI.

Dose mg BID	Mean	90%CI_Low	90%CI_Upper
Predicted AUC0-24h on Day 7 (ng/mL*h)			
60	244.1	-107.3	595.6
120	1254	902.7	1606
160	1928	1297	2558
Predicted AUC0-24h on Day 14 (ng/mL*h)			
60	219.9	-296.4	736.2
120	1605	1089	2122
160	2529	1602	3456

Figure 2 Predicted AUC0-24h following multiple doses with 90%CI

Predicted AUC0-24h on Day 7 with 90%CI



Predicted AUC0-24h on Day 14 with 90%CI

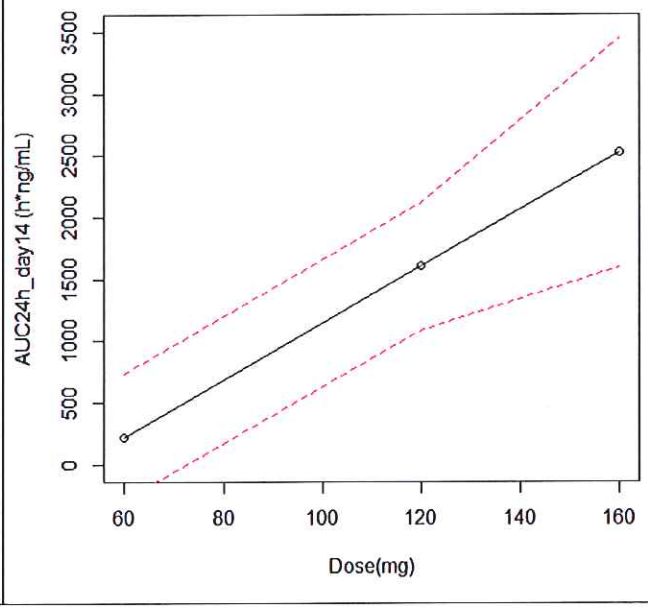
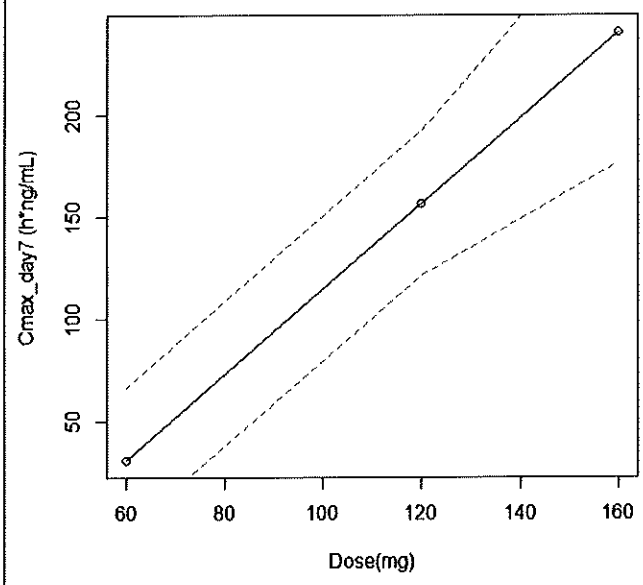


Table 3 Predicted Cmax following multiple doses with 90%CI.

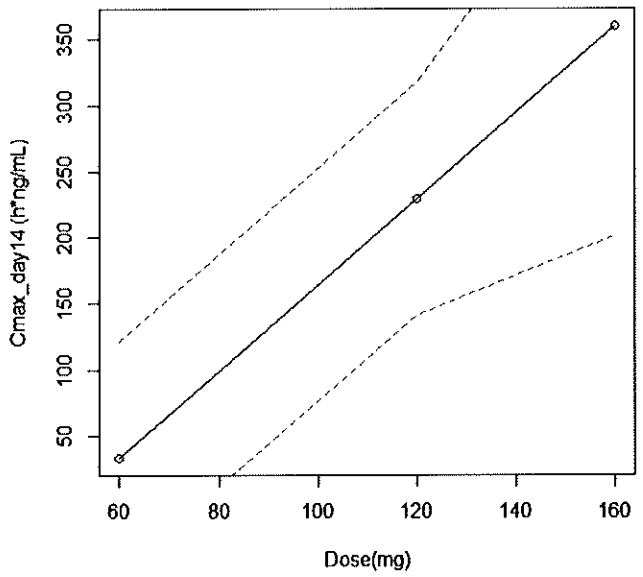
Dose mg BID	Mean	90%CI_Low	90%CI_Upper
Predicted Cmax on Day 7 (ng/mL)			
60	30.6	-5.0	66.2
120	156.3	120.7	191.9
160	240.1	176.2	304.0
Predicted Cmax on Day 14 (ng/mL)			
60	33.2	-54.8	121.3
120	229.1	141.0	317.1
160	359.6	201.5	517.7

Figure 3 Predicted Cmax following multiple doses with 90%CI.

Predicted Cmax on Day 7 with 90%CI



Predicted Cmax on Day 14 with 90%CI



Experimental Medicine Study: An fMRI study was conducted in collaboration with Drs. Royce Lee and Emil Coccaro at the Dept. of Psychiatry, University of Chicago. fMRI was used to test the hypothesis that orally administered SRX246, a V1a receptor antagonist, can block the effects of intranasally administered vasopressin on the brain (amygdaloid) response to threatening stimuli in human Subjects. This proved to be the case. The study was recently published (Lee 2013).

Background: While the specific actions of vasopressin on regional brain function have not been fully characterized, previous studies have shown effects of vasopressin signaling on the amygdala as well as other brain structures involved in the neural processing of social and emotional cues, including the temporoparietal junction, subgenual cingulate, and connected structures (Meyer-Lindenberg 2009, Rilling 2012, Thompson 2006, Zink 2010). Reactivity to social and emotional stimuli such as emotional faces in these brain regions has been previously linked to major depressive disorder (Leymen 2007). Coordinated activity in the anterior cingulate, amygdala, and temporoparietal junction is implicated in appraisal of social and emotional cues (Dodell-Feder 2011) and this circuit has been found to function abnormally in mood disorders (Drevets 2008, Price 2012).

Twenty-nine healthy male Subjects (ages 18-55) were enrolled in the study. They received a baseline fMRI scan using the task described below, and were then randomized to receive either oral SRX246 (120mg PO BID; n=15) or placebo (n=14) for a mean period of 7.3 days after which they were brought back for a second scanning session. Given our interest in vasopressinergic modulation of brain reactivity to social/emotional stimuli, an established, validated paradigm was chosen that has been utilized successfully in psychopharmacological research: implicit processing of emotional facial expressions (Norbury 2007, Coccaro 2007).

Oral SRX246 was administered for a mean of 7.3 days; SD = 1.3 (Minimum = 5 days; Maximum = 11 days). SRX246 was well tolerated; no serious or unexpected adverse events were noted. All AEs were mild (e.g., headache, tiredness) and no differences in rate of AES were found between placebo and drug. Exploratory pair-wise testing of laboratory and vital sign parameters with an uncorrected $p < 0.05$ significance level revealed no effect of drug, in accord with the 14-day MAD findings. Repeated Measures ANOVA of extracted parameter estimates from left amygdala detected a significant interaction of oral and intranasal drug in the left amygdala with threatening (angry faces) stimuli compared to neutral fixation ($F(1, 28) = 4.250$; $p = .05$). Subjects receiving oral placebo plus intranasal vasopressin (n=7) exhibited a BOLD response in the left amygdala significantly decreased relative to Baseline. In the SRX246-treated Subjects, this difference was not observed, indicating that oral drug blocked the effect of intranasal AVP in this area.

The study showed that SRX246 blunted effects of intranasal vasopressin on BOLD signal change in response to angry faces in the amygdala, temporoparietal cortex, and anterior cingulate. These findings indicate that SRX246 enters brain and acts on vasopressin receptors. The data also suggest that SRX246 affects brain circuits that are activated by social and emotional stimuli and highly relevant to irritability, anger, and aggression.

Preclinical toxicology. 13 Week Toxicology Studies in Rat and Dog: The NOAEL and exposure levels shown below provide a strong safety margin for the proposed 12 week dosing regimen in the tolerability trial. Summaries of these studies are incorporated into the Investigational Drug Brochure, with brief summaries provided below.

Rats. SRX246 was well tolerated and did not result in any clear, test article-related changes. Some animals exhibited audible and labored respiration and inflammation in the nasal turbinates, attributable to reflux following oral gavage dosing. This effect was not test article related, but was dose-dependent, because the concentration of drug and the volume of gavage fluid increased with dose.

Dogs. Daily oral administration of SRX246 via capsules was well tolerated at doses up to 30 mg/kg/day (equivalent to 16.7 mg/kg/day in a human), which was the NOAEL. In average US women and men who weigh 75 kg and 89 kg respectively, this translates into doses of 1252 and 1486 mg/day, considerably more than the proposed 160 mg PO BID dose. At the determined NOAEL, minimal histological changes in the liver and mild to moderate changes in liver enzymes were observed but importantly, there was no increase in bilirubin. The lack of any change in bilirubin led Covance, which conducted the study, and Dr. Michael Gallo, Professor, Toxicology Division, Environmental and Occupational Health Sciences Institute, Robert Wood Johnson Medical School, an expert consultant, to conclude that these findings are of questionable toxicological significance.

Metabolism Studies: Human Hepatic Microsomal Cytochrome P450 Isoenzyme Inhibition in vitro: SRX246 was tested for interactions with 5 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). The results showed no competition with CYP1A2 and CYP2C9 and minimal competition for CYP2C19 and CYP2D6 (IC50> 10 uM). For CYP3A4, the IC50 was 2.55 uM, still a very high concentration before any interactions were observed. These results strongly indicate that there is a very low risk of drug-drug interactions with SRX246 at the level of mitochondrial metabolism. Further, in vitro hepatocyte studies showed that SRX246 is metabolically stable in human hepatocytes with 85.4% remaining after 4 hrs. In rat hepatocytes, 25.7% remained after 240 minutes and in dog hepatocytes, 66.5% remained after 240 minutes.

2.3 Summary

Known and potential risks: HD patients differ from healthy volunteers in a number of ways. Weight loss, insomnia, depression, concomitant drug treatments, comorbid affective disorders, and reduced cognitive reserve are among the major differences to be expected in HD Subjects that can influence tolerability.

There is a weight loss in early stage HD (reference accessed at http://www.ncbi.nlm.nih.gov/pubmed/12427878). In men, mean BMI (±SE) was 25.90 ± 0.34 kg/m^2 among case Subjects and 27.68 ± 0.16 kg/m^2 among control Subjects ($p < 0.0001$). Corresponding values for women were 24.34 ± 0.43 kg/m^2 for case Subjects and 26.63 ± 0.21 kg/m^2 for control Subjects ($p < 0.0001$). In addition, when case Subjects with HD were restricted to those with disease duration of <1 year and absence of both chorea and dystonia, case Subjects still had lower BMI than control Subjects in both genders. Assuming that Subjects in the HD and control groups were approximately the same height, this suggests that the HD patients are 6-

8% lighter than controls. We do not feel that this small difference will necessitate a dose adjustment.

The NOAELs of SRX246 in rat and dog are 75 mg/kg/day and 30 mg/kg/day, respectively. The human equivalent numbers are 12.1 and 16.7 mg/kg/day or 1077 and 1463 mg/day in an 89 kg man. Since we propose to give Subjects a maximum of 320 mg of SRX246 per day (about one-third the lower NOAEL), the compound should be safe to use. We have not given normal volunteers 160 mg BID but we have given them 320 mg once a day safely in our SAD Phase I study. The 120 mg bid dose was safe and well tolerated in the MAD study. In the present trial, we escalate from 80 mg BID to 160 BID, with each escalation Subject to review of safety data. As shown above, we have modeled the 160 mg BID dose and estimates provide a good safety margin

Dose limiting toxicity was not observed in the single ascending dose (SAD) trial, multiple ascending dose (MAD) trial, or the Experimental Medicine (human fMRI) study. SRX246 was safe and well tolerated at the highest doses studied--320 mg in the SAD and 120 mg BID x 14 days in the MAD studies. The adverse event profile of SRX246 in humans is not fully known, and adverse reactions may occur following treatment with SRX246. All Subjects participating in clinical trials will be observed closely for adverse reactions potentially related to study drug administration.

No clinical drug interaction studies have been performed with SRX246. Preliminary data from an in vitro metabolism study are available: when SRX246 was incubated with human hepatocytes, most of the drug remaining afterwards was unchanged. It was concluded that there is no significant in vitro hepatic metabolism of SRX246. This supports the conclusion that SRX246 has a low probability of being involved in drug-drug interactions mediated by its interaction with P450 enzymes as does the fact that SRX246 has been shown to have little cytochrome P450 isoenzyme inhibition activity.

In the Phase I and Phase II clinical studies of SRX246 that have been conducted to date, drug treated Subjects did not have AEs in excess of those uncovered in Subjects taking placebo, and the nature of the AEs were similar in both cases. The following problems were reported in Subjects taking SRX246: tachycardia, conjunctival hyperemia, upper abdominal pain, diarrhea, epigastric discomfort, gastroesophageal reflux, lip pain, nausea, vomiting, and chest pain. Almost all of these were mild in intensity. The problems were not dose related. Thus, at this point, there are no special precautions that need to be given to trial Subjects. Any that emerge during the course of the study will be communicated to the sites and IRBs.

3 STUDY DESIGN

This is a 3-arm, multicenter, randomized, placebo-controlled, double-blind, 12 week, dose escalation study of SRX246 in irritable Subjects with early symptomatic HD.

Following an initial screening visit, Subjects fulfilling the study inclusion and exclusion criteria will enter a pre-treatment screening phase to permit evaluations to confirm eligibility for inclusion into the study. This screening phase will be no longer than 30 days. At the completion of the screening period, eligible Subjects will be randomized at baseline visit to receive either placebo or final doses of SRX246 of 120 mg twice daily or 160 mg twice daily during the double-blind treatment phase. At baseline, Subjects in the active groups will receive 80 mg twice daily for 2 weeks, then escalate to 120 mg twice daily for 4 weeks. Then one group of Subjects will continue to take 120 mg of SRX246 twice daily for an additional 6 weeks, and the second group of Subjects will increase their dose to 160 mg of SRX246 twice daily for 6 weeks. Total dosing duration is 12 weeks.

Subjects in the placebo group will receive a similar number of capsules that are identical in appearance to the capsules that contain SRX246 during the trial, in order to preserve the blind.

In all groups, dose escalation will occur (stepwise) if patients have not experienced dose-limiting adverse effects. Patients who cannot tolerate their final dose of drug (or placebo) can have this dose reduced without compromising the blinding.

Subjects will have periodic visits either "in-person" or by "telephone". Their eDiary will prompt them to take their capsules twice a day and ask whether they did so. They and their Study Partner will also be asked to answer daily questions having to do with irritability and behavior.

A summary of the visits and assessments to be conducted is provided in APPENDIX A.

4 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

1. Male and female Subjects aged 18 years or older.
2. Subjects must have clinical features of HD, which can include motor, cognitive, or behavioral symptoms.
3. A confirmatory family history of HD; OR CAG repeat expansion ≥ 37.
4. Total Functional Capacity (TFC) score of 5-13.
    a. If TFC<7, an assessment of capacity to consent will be required.
5. Evidence of irritability; a score of at least 2 or greater on the severity measure of either the UHDRS Irritability question (30b) or Aggression question (Disruptive or Aggressive Behavior, 31b).
6. Medications prescribed for mood, behavior, or neurologic symptoms must be stable for 30 days prior to the Baseline Visit.
7. Women of childbearing potential (i.e., those not postmenopausal or surgically sterile) must have a negative pregnancy test, be non-lactating and use adequate contraception methods during the study. Adequate birth control includes: abstinence; oral, implanted or injected contraceptives, e.g., birth control pills; intra-uterine device; barrier (vaginal ring or diaphragm/cervical cap with spermicide); transdermal patch. Reliable contraception must have been in use 30 days prior to the Baseline Visit. Partner(s) contraception (e.g., male partner with vasectomy or other surgical contraception) is acceptable.
8. Men must agree not to father a child during the study and one month after and to use contraception. Barrier with spermicide or surgical contraception is acceptable. Partner(s) contraception (e.g., female partner taking birth control pills or surgically sterile) is acceptable.
9. Subjects must be able to swallow study drug capsules whole.
10. Sufficient English skills to complete all assessments without assistance of an English language interpreter. Subjects with HD who cannot read or write might qualify for enrollment in the study. Site PIs will have to decide in each case whether the Subject can understand and fully participate with help from his/her Study Partner.
11. Availability of a responsible Study Partner who has good English skills, is familiar with the Subject, and is able and willing to comply with all required study procedures, ensuring that the Subject attends all study visits and takes the study medicine as instructed. The Study Partner must spend time with the Subject a minimum of 4 times per week on 4 separate days, and must monitor the Subject's compliance and adverse events, participate in Study Partner assessments, and use the eDiary.
12. Subject has provided written, informed consent or, if Subject lacks the capacity to provide informed consent, a legally authorized representative (LAR) has provided written informed consent and the Subject has provided assent.

4.2 Exclusion Criteria

1. Any significant neurologic disease other than HD at Screening.
2. Severe psychotic features or other severe psychiatric symptoms within the last three months which could lead to difficulty complying with the protocol.
3. History of active alcohol or substance abuse within the past two years or Subject is unable to refrain from substance abuse throughout the study.

4. Any chronic disability, significant systemic illness or unstable medical condition at Screening or Baseline that could lead to difficulty complying with the protocol.
5. Use of any investigational drugs within 30 days of Screening.
6. Subject has known allergy to any of the components of study medication.
7. Subject is currently pregnant, breast-feeding and/or lactating.
8. Subject acknowledges present use of illicit drugs at Screening.
9. Active suicidal ideation in the judgement of the Investigator.

4.3 Subject Withdrawal Criteria

A Subject may withdraw without bias or be withdrawn from the study for the following reasons:

Administrative

1. Withdrawal of consent by Subject or by LAR, if applicable
2. Request of Study Sponsor or Principal Investigator
3. Request of primary care physician
4. Non-compliance
5. Failure to meet entry criteria
6. Pregnancy
7. Protocol deviation
8. Subject deemed lost to follow up/failure to return
9. Early termination of study
10. Other

Adverse Event

1. Worsening of the disease under study
2. Worsening of pre-existing disease (other than disease under study)
3. Intercurrent illness
4. Death
5. Major/clinically significant alteration in laboratory values after beginning study drug
6. Other adverse event

4.4 Study Enrollment Procedures

Subjects will be recruited from NeuroNEXT investigative sites in the United States. Sites will be responsible for obtaining written consent from each potential Subject after adequate explanation of the purpose, study procedures, and any risks associated with the study. Subjects will be asked to identify a Study Partner who will be asked to participate in the study by completion of selected assessments as listed in the schedule of activities (Appendix A).

Treatment for each Subject will be assigned by a randomized code. A block randomization scheme will be used to ensure approximately even distribution of Subjects in treatment groups at each site.

4.4.1 Subject Recruitment and Retention

Participants will be recruited from clinics at participating NeuroNEXT Network sites. Postings will be placed on appropriate websites. Flyers and other promotional materials about the study will be developed for use by the NeuroNEXT clinical sites or partner organizations (see the organizations below). Webinars will be conducted for participant recruitment as needed.

Interested participants will be contacted by the investigators or their staff and invited to participate. These recruitment strategies will include a mechanism by which the patients can provide their contact information. The NeuroNEXT Recruitment and Retention Committee will also advise about recruitment strategies. The Huntington Study Group (HSG), The Huntington Disease Society of America, the Cure Huntington Disease Initiative (CHDI), the Indiana HD Registry, and several HD family operated social media outlets provide potential collaborations to enable advertising and recruitment.

The fact that there are two active (SRX246) arms and one placebo arm increases the likelihood that Subjects will be on study drug, which has helped with recruitment and retention in past studies of HD. Site PIs should be careful to stress that the drug may not prove to be helpful to participants, however, and that the treatment will be of limited duration. Subjects who cease taking study drug (or placebo) will be encouraged to continue to participate (off treatment) in the study.

4.4.2 Screening Logs

Screening logs to document reasons for ineligibility and reasons for nonparticipation of eligible Subjects will be stored centrally at the NeuroNEXT Data Coordination Center. Information about screening failures and successes will be compiled and reviewed monthly by the operations committee so that feedback can be provided to sites in real time and so that marketing strategies can be adjusted as needed.

4.4.3 Informed Consent

Written informed consent will be obtained from each study participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form approved by the NeuroNEXT Central Institutional Review Board (CIRB), which will be signed by the participant with the date of that signature indicated. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50. HIPAA guidelines for confidentiality and the principles of medical ethics will be adhered to during the study. An informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks must be read and/or explained to each Subject or Study Partner. Each Subject (or Subject's legally authorized representative (LAR), if applicable) and Study Partner will sign such an informed consent form. (It is acceptable for the LAR to serve as the Study Partner.) In this consent, the study must be adequately described. All the procedures Subjects will need to do, and how their confidentiality will be maintained must be detailed. In the case of a telephone interview, the caller must explicitly ask for their consent to participate.

The Subject and Study Partner must be assured of the freedom to decline entry or withdraw from participation in the study at any time. It is the Investigator's responsibility to make sure that the Subject and/or LAR understands what she/he is agreeing to and that written informed consent is obtained before the any protocol-defined procedures including screening procedures. It is also the Investigator's responsibility to retain the original signed consent form

and provide each Subject with a copy of the signed consent form. The consent process for each Subject or Study Partner who signs informed consent will be documented in the Subject's source material (e.g., research file, research progress note) and should include the title of the study, that the consent was discussed with an opportunity for questions and answers, how the Subject demonstrated comprehension, that the consent was signed prior to the first study procedure, and that the Subject received a signed copy of the consent.

4.4.4 Study Partner Consent for Completion of Questionnaires

The study includes outcome measures completed at Baseline and designated follow up visits by the Study Partner. It is very strongly encouraged that Study Partners, at a minimum, attend the Baseline, week 6, and week 12 visits in-person. The Study Partner will also be asked to upload answers to eDiary questions. The Study Partner will have the purpose of the questionnaires explained by study staff at the Baseline visit and will be given a chance to read the informed consent, ask questions, and have any questions answered prior to signing the consent form. The Study Partner consent will be completed at Screening, unless a Study Partner has not yet been designated or is not present, in which case will be conducted at Baseline. The Study Partner is very strongly encouraged to be present at each specified in-person visit but can complete assessments by phone if attending in person is not feasible. The Study Partner may be asked to participate in additional phone assessments, should they be required.

4.4.5 Assent

Children (age less than 18) will not be allowed to participate in this study. HD patients who cannot reasonably be expected to provide informed consent or are found by assessment of the site investigator to lack sufficient capacity will be asked to assent after the study has been explained to them in terms they can readily understand and after they have been given an opportunity to ask any questions they may have. In this event the HD Subject will be asked to signify their assent by co-signing the consent form executed by his/her LAR.

4.4.6 Randomization/Treatment Assignment

The treatment for each Subject will be assigned by a randomized code. A block randomization scheme will be used to ensure approximately even distribution of Subjects in treatment groups at each site.

5 STUDY INTERVENTIONS/STUDY MEDICATION/STUDY DRUG OR DEVICE

5.1 Study Medication

Investigational Study Drug:	SRX246 or Placebo
Route of Administration:	Oral
Presentation:	Hard Gelatin Capsules
Storage Condition:	Store at room temperature (15-30°C, 59-86°F)

The Clinical Materials Services Unit (CMSU), at the University of Rochester will provide primary labeling and secondary packaging, labeling and distributions services. The study drug will be dispensed by appropriately qualified site study staff as indicated on the delegation of authority log. Subjects will self-administer the study drug at home following the directions given to them in the clinic. Outpatient Subjects will be instructed to take these capsules by mouth twice a day (morning and evening), with plenty of water, with no special requirements for taking with food. The SRX246 capsules and placebo capsules will be provided by Azevan.

5.2 Handling of Study Medications/Interventions

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the research pharmacy (where applicable) is responsible for ensuring product accountability records are maintained throughout the course of the study. The accountability records will include details of SRX246 study drug or placebo received and dispensed to Subjects, including batch and/or ID numbers. Subjects will be instructed to return all unused study drug to the clinical trial site at each visit. All unused capsules must be kept until reconciliation of delivery records with accountability logs by the monitor. After the monitor has performed accountability, the site will be instructed to either destroy the remaining study medication or return it to the Central Pharmacy or manufacturer. An accounting must be made of any drug deliberately or accidentally destroyed. Discrepancies between the amount of SRX246 study drug/placebo received and dispensed drug must be reconciled.

5.3 Concomitant Interventions

There will be no restrictions on use of concomitant medications and of medication interventions during the course of the study, though all medications and doses and indications will be reviewed and recorded at screening and at all visits. Information on any changes in concomitant medications will be recorded at each visit. The use of new medications or adjustment of concomitant medications for mood or behavior is strongly discouraged unless deemed clinically necessary by the subject's treating clinician in response to a severe adverse event considered by the investigator to jeopardize the safety of the subject or others (e.g., significantly worsening depression, behavior, or psychosis). These severe adverse events and any medication changes related to them must be reported to the project manager within 24 hours and source documentation (e.g., clinic notes) for the clinical findings and medication changes must be included in the study record.

5.4 Subject compliance

At each study visit, the site Investigator and/or Study Coordinator will assess the Subject's compliance with the study requirements. This will include checks of protocol compliance, including use of study drug, in order to assess the reliability of Subject-generated data. Subjects who fail to comply with the study requirements may be withdrawn from the study.

6 STUDY PROCEDURES

Following is a detailed description of the study procedures. A summary of the visits and assessments to be conducted is provided in APPENDIX A.

6.1 Visit SC (Screening) Day -30 to 0

Screening procedures will take place within 30 days of the Baseline visit. During this visit, the Subject (and Study Partner) will be thoroughly informed about all aspects of the study, including all scheduled visits and activities, and will be requested to sign and date the informed consent prior to performing any study-related procedures.

Subjects will be assessed for study eligibility by the site Investigator. All the inclusion criteria must be met and none of the exclusion criteria may apply. All the results from the screening procedures must be available before determining a Subject's eligibility for the study.

The following procedures will be performed at the screening visit (this visit may take approximately 4 hours):

- Obtain written informed consent from Subject
- Obtain written informed consent from Study Partner or ask Subject to identify an individual by the time of return for the Baseline Visit, if not already identified at this visit.
- Assign Subject ID Number and CTCC Unique Identification Number, as applicable.
- Obtain screening demographics from Subject (date of birth, gender, race).
- Obtain screening demographics from Study Partner (date of birth, gender, race).
- Collect a minimum of 5mL of urine in a sterile plastic container for a urine drug abuse screening test (i.e., NIDA-5).
- Conduct UHDRS assessment (Huntington Study Group 1999).
- Total Functional Capacity (TFC) score must be between 5-13, inclusive.
    - TFC is <7, an assessment of capacity to consent will be required.
- Evidence of irritability must be met, i.e., a score of at least 2 or greater on the severity measure of either the UHDRS Irritability question (30b) or the Aggression question (Disruptive or Aggressive Behavior, 31b).
- Perform clinical assessment for suicidal ideation with the Columbia-Suicide Severity Rating Scale (C-SSRS; Posner 2008).
- Review Inclusion/Exclusion criteria.
- Review the Subject's medical history to assess for possible exclusionary conditions. Medical histories should include baseline symptoms, ongoing illnesses, other chronic conditions, surgical history, review of currently used medications, as well as any other important information that may affect the conduct of the study.
- Perform a complete Physical Examination, including neurological.
- Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute), and obtain body temperature (°C).
- Record height (cm) and weight (kg) measurements.
- Perform a resting 12-Lead EKG.

- Collect blood samples for routine hematology/serum chemistry, and for a serum pregnancy test for women of childbearing potential refer to Section 6.13.5 for required tests).
- Collect urine for routine urinalysis (refer to Section 6.13.5 for required tests).
- For women of childbearing potential and sexually active males, review acceptable birth control methods that must be used during the study.

For all Subjects who signed an informed consent, the screening and demographic data is required. For Subjects who sign consent but do not enter the study, data may also be submitted for any additional assessments that were completed.

If a Subject does not meet all eligibility requirements and returns to be re-screened, the Subject must be re-consented if it has been more than 60 days from the initial date of consent. All evaluations must be repeated at re-screening.

6.2 Visit BL (Baseline) Day 0

The following procedures will be performed within 30 days from the screening visit (this visit may take about 3 hours):

- Review the Subject's written informed consent; and, obtain written informed consent from Study Partner, if not performed at screening visit.
- Obtain screening demographics from Study Partner (date of birth, gender, race), if not performed at screening visit.
- Conduct final review of eligibility (prior to first dose), including confirmation of laboratory test results from the Screening assessment. Subjects must continue to meet all enrollment criteria at the Baseline Visit.
- Collect blood samples for CAGn genotyping and DNA storage (refer to University of Rochester Medical Center Lab Manual for sample handling and processing requirements).
- Collect a urine sample and conduct a pregnancy test for women of childbearing potential.
- For women of childbearing potential and sexually active males, review acceptable birth control methods that must be used during the study.
- Assess the Subject for Concomitant Medication use.
- Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
- Record the Subject's body temperature (°C).
- Perform a resting 12-Lead EKG.
- Perform clinical assessment for suicidal ideation with the CSSRS.
- Conduct UHDRS assessment (Huntington Study Group 1999).
- Total Functional Capacity (TFC) score must be between 5-13, inclusive.
    - TFC is <7, an assessment of capacity to consent will be required.
- Evidence of irritability must be met, i.e., a score of at least 2 or greater on the severity measure of either the UHDRS Irritability question (30b) or the Aggression question (Disruptive or Aggressive Behavior, 31b).
- Assess the Subject using the Clinical Global Impression – Severity of Illness (CGI-S).
- Administer the Problem Behaviors Assessment short form (PBA-s) to the Subject and Study Partner, together.

- Administer the Aberrant Behavior Checklist (ABC), irritability subscale to the Study Partner.
- Administer the Cohen-Mansfield Agitation Inventory (CMAI) to the Study Partner.
- Administer the HD Irritability Scale (IS) to the Subject and Study Partner, separately.
- Administer the HD QoL to the Subject and Study Partner, together.
- Administer the Caregiver Burden Questionnaire to the Study Partner.

After the Baseline (BL) visit activities have been completed and the Subject is deemed eligible to participate in the study, the site Coordinator will enroll the Subject into the study by accessing the online data capture tool for enrollment. Once the system confirms requirements for eligibility have been met, a random Enrollment ID number corresponding to study drug will be generated and assigned to the Subject. Once the Subject has been randomized, the site will complete the following additional activities:

- Administer first dose of study drug (80mg BID SRX246 dose or Placebo).
- Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute) approximately 1-2 hours after first dose (estimated time to Cmax).
- Inquire about any immediate side effects (e.g., nausea, dizziness, GI discomfort).
- Dispense study drug supplies (80mg BID SRX246 dose or Placebo) for the next 2 weeks, and complete drug accountability/ management log.
- Instruct Subject and Study Partner about correct administration of study drug, remind the Subject to begin taking capsules twice daily (in the morning and in the evening), beginning the morning of the next day.
- Instruct Subject and Study Partner to bring unused study drug to each study visit, and to immediately report any AEs to the Investigator or Coordinator.
- Provide the phone- or tablet-based eDiary and instruct the Subject and Study Partner on its use.

6.3 Visit 01 (Week 2) Day 14±5

The following procedures will be performed during this visit (this visit may take about 2 hours):

- Assess the Subject for possible AEs and Concomitant Medication use.
- Review amount of study drug returned and assess compliance.
- Review the use of the eDiary and encourage the Subject and Study Partner to make and upload entries two times per day.
- Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
- Record the Subject's body temperature (°C).
- Perform a resting 12-Lead EKG.
- Perform clinical assessment for suicidal ideation with the CSSRS.
- Collect blood samples for routine hematology/serum chemistry (refer to Section 6.13.5 for required tests).
- If two tubes not collected at Baseline Visit (Day 0), collect blood samples for CAGn genotyping and/or DNA storage (refer to University of Rochester Medical Center Lab Manual for sample handling and processing requirements).
- Collect urine for routine urinalysis (refer to Section 6.13.5 for required tests).

- Dispense study drug and instruct the Subject and Study Partner about correct administration of study drug (i.e., change in dose to 120 mg BID SRX246 or Placebo).
- Instruct Subject and Study Partner to bring unused study drug to each study visit, and to immediately report any AEs to the Investigator or Coordinator.

6.4 Visit T1 (Week 4) Day 28±5

This visit will be a Telephone follow-up to perform the following (this may take about 15 minutes):

- Assess the Subject for possible AEs and Concomitant Medication use.
- Inquire about study drug compliance - assess whether study drug is being taken properly by the Subject (and if applicable, Study Partner) self-report. Subjects who do not experience intolerability will remain on their daily dose of study drug.
- Instruct Subject and Study Partner to bring unused study drug to each study visit, and to immediately report any AEs to the Investigator or Coordinator.
- Review the use of the eDiary and encourage the Subject and Study Partner to make and upload entries two times per day.

6.5 Visit 02 (Week 6) Day 42±5

The following procedures will be performed during this visit (this visit may take about 3 hours):

- Assess the Subject for possible AEs and Concomitant Medication use.
- Review amount of study drug returned and assess compliance.
- Review the use of the eDiary and encourage the Subject and Study Partner to make and upload entries two times per day.
- Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
- Record the Subject's weight (kg) and obtain body temperature (°C).
- Perform a resting 12-Lead EKG.
- Collect blood samples for routine hematology/serum chemistry, and for a serum pregnancy test for women of childbearing potential (refer to Section 6.13.5 for required tests).
- If two tubes not collected at Baseline Visit (Day 0), collect blood samples for CAGn genotyping and/or DNA storage (refer to University of Rochester Medical Center Lab Manual for sample handling and processing requirements).
- Collect urine for routine urinalysis (refer to Section 6.13.5 for required tests).
- Perform clinical assessment for suicidal ideation with the CSSRS (Since Last Visit).
- Conduct UHDRS assessment (Huntington Study Group 1999).
- Total Functional Capacity (TFC) score must be between 5-13, inclusive.
    - TFC is <7, an assessment of capacity to consent will be required.
- Assess the Subject using the Clinical Global Impression – Improvement (CGI-I).
- Administer the Problem Behaviors Assessment short form (PBA-s) to the Subject and Study Partner, together.
- Administer the Aberrant Behavior Checklist (ABC), irritability subscale to the Study Partner.
- Administer the Cohen-Mansfield Agitation Inventory (CMAI) to the Study Partner.
- Administer the HD Irritability Scale (IS) to the Subject and Study Partner, separately.
- Administer the HD QoL to the Subject and Study Partner, together.

- Administer the Caregiver Burden Questionnaire to the Study Partner.
- Dispense study drug and instruct the Subject and Study Partner about correct administration of study drug (i.e., either remaining at 120 mg BID SRX246 or Placebo, change in dose to 160 mg BID SRX246 or Placebo, or possible dose reduction based on intolerability).
- Instruct Subject and Study Partner to bring unused study drug to each study visit, and to immediately report any AEs to the Investigator or Coordinator.
- At the time of scheduling the next visit, remind the Subject not to take drug (or placebo) on the morning of the next visit, that the study drug will be taken in the clinic during the next visit to enable sparse PK sampling.

6.6 Visit 03 (Week 8) Day 56±5

The following procedures will be performed during this visit (this visit may take about 4 hours):

- Assess the Subject for possible AEs and Concomitant Medication use.
- Review amount of study drug returned and assess compliance.
- Review the use of the eDiary and encourage the Subject and Study Partner to make and upload entries two times per day.
- Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
- Record the Subject's body temperature (°C).
- Perform a resting 12-Lead EKG.
- Collect blood samples for routine hematology/serum chemistry (refer to Section 6.13.5 for required tests).
- If two tubes not collected at Baseline Visit (Day 0), collect blood samples for CAGn genotyping and/or DNA storage (refer to University of Rochester Medical Center Lab Manual for sample handling and processing requirements).
- Collect urine for routine urinalysis (refer to Section 6.13.5 for required tests).
- Prepare the subject for PK blood sampling for the sparse PK study. Subjects will have been prompted to note the time at which the dose of study compound was taken the night before (either in their eDiaries or on a piece of paper), and to bring their dose for the morning of the visit with them but not to take it until they are instructed to do so.
    - Blood will be drawn as soon as the patient arrives in the clinic; then the morning dose of drug should be given and the time recorded.
    - Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute) approximately 1-2 hours after taking the morning dose (estimated time to Cmax).
    - Two (2) hours later (time to be recorded), blood will be drawn again.
    - Process the PK samples as directed in the University of Rochester Medical Center Lab Manual
- Dispense study drug and instruct the Subject and Study Partner about correct administration of study drug (i.e., either 120 mg BID SRX246, 160 mg BID SRX246 or Placebo, or possible dose reduction based on intolerability).
- Instruct Subject and Study Partner to bring unused study drug to each visit, and to immediately report any AEs to the Investigator or Coordinator.

- If not performed during this Visit, at the time of scheduling the next visit, remind the Subject not to take drug (or placebo) on the morning of the next visit, that the study drug will be taken in the clinic during the next visit to enable sparse PK sampling.

6.7 Visit 04 (Week 10) Day 70±5

The following procedures will be performed during this visit (this visit may take about 2 hours, if PK required this visit may take about 3 hours):

- Assess the Subject for possible AEs and Concomitant Medication use.
- Review amount of study drug returned and assess compliance.
- Review the use of the eDiary and encourage the Subject and Study Partner to make and upload entries two times per day.
- Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
- Record the Subject's obtain body temperature (°C).
- Perform a resting 12-Lead EKG.
- Collect blood samples for routine hematology/serum chemistry (refer to Section 6.13.5 for required tests).
- If two tubes not collected at Baseline Visit (Day 0), collect blood samples for CAGn genotyping and/or DNA storage (refer to University of Rochester Medical Center Lab Manual for sample handling and processing requirements).
- Collect urine for routine urinalysis (refer to Section 6.13.5 for required tests).
- If not performed during Visit 03, prepare the subject for PK blood sampling for the sparse PK study.
- Dispense study drug and instruct the Subject and Study Partner about correct administration of study drug (i.e., either 120 mg BID SRX246, 160 mg BID SRX246 or Placebo, or possible dose reduction based on intolerability).
- Instruct Subject and Study Partner to bring unused study drug to each visit, and to immediately report any AEs to the Investigator or Coordinator.

6.8 Visit 05 (Week 12) Day 84±5

The following procedures will be performed during this visit (this visit may take about 4 hours):

- Assess the Subject for possible AEs and Concomitant Medication use.
- Retrieve all supplies of the study drug, review amount of study drug returned and assess compliance.
- Retrieve the eDiary and ensure all data have been transmitted.
- Perform a Complete Physical Examination, including neurological.
- Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
- Record the Subject's weight (kg) and obtain body temperature (°C).
- Perform a resting 12-Lead EKG.
- Collect blood samples for routine hematology/serum chemistry, and for a serum pregnancy test for women of childbearing potential (refer to Section 6.13.5 for required tests).
- Collect blood samples for CAGn genotyping and/or DNA storage if both not collected at Baseline (refer to University of Rochester Medical Center Lab Manual for sample handling and processing requirements).

- Collect urine for routine urinalysis (refer to Section 6.13.5 for required tests).
- Perform clinical assessment for suicidal ideation with the CSSRS (Since Last Visit).
- Conduct UHDRS assessment (Huntington Study Group 1999).
- Total Functional Capacity (TFC) score must be between 5-13, inclusive.
    - If TFC is <7 an assessment of capacity to consent will be required.
- Assess the Subject using the Clinical Global Impression – Improvement (CGI-I).
- Administer the Problem Behaviors Assessment short form (PBA-s) to the Subject and Study Partner, together.
- Administer the Aberrant Behavior Checklist (ABC), irritability subscale to the Study Partner.
- Administer the Cohen-Mansfield Agitation Inventory (CMAI) to the Study Partner.
- Administer the HD Irritability Scale (IS) to the Subject and Study Partner, separately.
- Administer the HD QoL to the Subject and Study Partner, together.
- Administer the Caregiver Burden Questionnaire to the Study Partner.
- Upon confirmation that the Subject is medically stable and all study procedures have been completed, discharge the Subject from the visit and instruct the Subject and Study Partner to immediately report any AEs to the Investigator or Coordinator.

6.9 Visit T2 (Follow-Up) Day 91±5

This visit will be a Telephone follow-up to perform the following (this may take about 15 minutes):

- Assess the Subject for possible AEs and Concomitant Medication use.
- Upon confirmation that the Subject is medically stable and all study procedures have been completed, discharge the Subject from the study.

6.10 Unscheduled Visits or Telephone Contacts (Visit UXX or TXX)

An unscheduled visit (UXX) or telephone contact (TXX) may be performed at any time during the study at the Subject's or Study Partner's request or as deemed necessary by the site Investigator. The date and reason for the UXX or TXX, as well as the results of any additional testing, will be recorded in the source documentation. Reasons may include, but are not limited to, the need to repeat a suspect laboratory safety test, a potential severe side effect, worsening of behavioral symptoms, multiple missed doses of medication.

6.11 Premature Withdrawal (PW)

Subjects have the right to withdraw from the study at any time without prejudice. The site Investigator may withdraw study drug from a Subject in the study in the event of intercurrent illness, adverse events, other reasons concerning the health or well-being of the Subject, or in the case of lack of cooperation, non-compliance, protocol violation or other administrative reasons. Premature withdrawal will be implemented in the case of emergency disclosure of drug treatment (i.e., unblinding).

A Subject may withdraw or be withdrawn from the study for the following reasons:

Administrative

1. Withdrawal of consent
2. Request of [Sponsor or Principal Investigator]

3. Request of primary care physician
4. Non-compliance
5. Failure to meet entry criteria
6. Pregnancy
7. Protocol deviation
8. Subject deemed lost to follow up/failure to return
9. Early termination of study
10. Other

Adverse Event

1. Worsening of the disease under study
2. Worsening of pre-existing disease (other than disease under study)
3. Intercurrent illness
4. Death
5. Major/clinically significant alteration in laboratory values after beginning study drug
6. Other adverse event

In the event of premature withdrawal from the study, every effort should be made to obtain an in-person final visit, which should include the same procedures as Visit 05 (Week 12). This can be performed whether or not the withdrawal is determined at a regularly scheduled study visit or at an unscheduled visit. Visit T2 should still be performed 7±5 days after the final in-person visit.

Should a scheduled in-person visit be impossible, conduct as many of the verbal assessments as possible, with special emphasis on obtaining information on possible AEs, and arrange for return of study drug.

Reasons for withdrawal of the Subject prior to completion of the study must be stated in the CRF and in the site source documentation for all study Subjects who were enrolled in the study. The CCC and the IMM must be informed within 24 hours of all study Subjects who are withdrawn due to an adverse event.

6.12 Dosage Adjustments

Dosage adjustments (dose reductions and suspensions) will be allowed if warranted, in the clinical judgment of the site Investigator in consultation with the medical monitor. Restarting study drug after suspensions will be allowed. The overall goal is to encourage each Subject to reach the target dosage and complete the study. The CTCAE Version 4.0 may be used as a reference guide for dosage adjustments. Grade 2 or greater adverse effects for laboratory values and clinical events should be considered when evaluating intolerability and determining whether a dose reduction is warranted. While these criteria will be used as a guide, site investigators, in consultation with the medical monitor, will ultimately make the decisions about dosage adjustments.

6.12.1 Dosage Reduction

Dosage reductions are permitted during the study due to tolerability issues or adverse events that are thought to be related to study drug. In the first two weeks of the trial, subjects who cannot tolerate the drug will receive no more capsules but will be encouraged to continue participating in the study. Reductions can be performed once between study weeks 2 and 6, and twice between study weeks 6 and 12. The project manager should be notified in this case to discuss and confer with the protocol PI and/or medical monitor if necessary. A dosage reduction is accomplished by lowering the total daily dose (as deemed necessary by the site Investigator) until symptoms resolve or reduced dosage is tolerated by the Subject. Dose reduction can only be performed up to a maximum of 2 times, until the Subject is removed from further dosing with study drug.

6.12.2 Dosage Suspension

Administration of the study drug may be interrupted for intolerable adverse effects thought to be related to study drug, intercurrent illnesses, or surgery at any time during the study. These situations will be handled on a case-by-case basis in consultation with the protocol PI or medical monitor. A suspension may last up to one week. Subjects will be removed from the study if a suspension is predicted to last longer than one week (e.g., a scheduled surgery with long recovery period or a severe illness such as a stroke that is unlikely to resolve in less than one week). Study drug suspensions for planned travel, holidays, or vacations of the Subject (or Study Partner) are to be avoided.

6.12.3 Premature Drug Discontinuation

There is no downward titration necessary when the study drug is permanently discontinued. If a Subject cannot tolerate the dosing regimen, study drug will be permanently discontinued.

6.12.4 Restarting Study Drug after Premature Drug Discontinuation

In the event that the study drug was discontinued prematurely for reasons unrelated to safety, restarting the study drug will be allowed if the Subject wishes to resume taking it and this is deemed appropriate by the site Investigator in consultation with the medical monitor. An unscheduled in-person visit will be conducted to complete required assessments unless the intended visit would occur during a scheduled visit window. Subjects must continue to meet all inclusion and exclusion eligibility criteria prior to restarting study drug. The Subject will complete study visits according to the relevant Schedule of Activities and in relation to the Subject's baseline evaluation date (not according to time on study drug).

6.12.5 Missed Doses

Subjects should not take additional doses to make up for missed doses. For example, if a Subject forgets to take the morning dose it should not be added to the next scheduled dose in the evening. If a dose is missed but there is still time to have approximately 8 hours before the next dose, then the missed dose should be taken.

6.12.6 On Study/Off-Intervention Evaluations

Every possible effort should be made by the site PI to encourage Subjects who are no longer taking study drug to remain in the study. They should explain that continued participation will teach us more about HD and behavioral scales that can be used to test drugs in the future.

When Subjects decide to go off the study drug, it will be a reportable event and the project manager will discuss the reasons for this with site staff to learn the specifics in each case and provide advice on an individual basis about the best ways to keep the Subject engaged in the project. (These Subjects and their physicians will not be told whether they were given SRX246 or placebo.)

6.12.7 Off-Study Requirements

Adverse events will be followed up to 30 days of study completion (including premature withdrawal) or until the site Principal Investigator deems the condition to have resolved or the condition has stabilized (whichever occurs first).

6.12.8 Pregnancy

Women who become pregnant while in the study will have the study drug withdrawn immediately, will be asked to return for a final in-person evaluation, and will be followed according to adverse event reporting procedures until birth or conclusion. Generally, follow-up will not exceed 8 weeks following the estimated delivery date.

6.13 Special Instructions and Definitions of Evaluations

6.13.1 Protocol Deviations

Protocol deviations are instances where the IRB approved protocol has not been followed that do not have an impact on Subjects' rights, safety, or well-being, but could affect the

completeness, accuracy, and reliability of the study data. Even minor changes, divergences, or departures from the study design that are under the Investigator's control should be reported (see below).

A protocol **violation** is an accidental or unintentional change to the IRB approved protocol that places one or more participants at increased risk or has the potential to occur again. **Significant (Major) deviations** are unapproved changes from the protocol that significantly affect the safety of the Subject, the scientific quality of the study, or the safety of researchers (e.g., deviations from eligibility criteria that are intended to exclude those for whom the study poses unreasonable risks, failure to perform safety assessments intended to detect pregnancy or drug toxicity at the right times). Even with well-written, IRB approved protocols; well-trained and qualified clinical Investigators; internally consistent, coherent, study-specific standard operating procedures; and an attitude of wanting to be compliant, deviations/violations can occur.

Subject non-compliance occurs when, despite the best efforts of the research staff, the Subject fails to follow the protocol. Instances of non-compliance (e.g., taking too much study drug) can cause safety issues (significant deviations) if they occur in a significant number of Subjects, and they can result in missing data. Failure to keep appointments, communication failures, unreliable study drug consumption and accountability, and failure to keep diaries or other assessments are among the deviations that raise concern about continued participation. If reminders, counseling, and instruction do not help (i.e., if a Subject's deviations become too numerous, severe, or extensive) the PI and project team may consider withdrawing a Subject from the study.

Descriptions of deviations and violations are reported to the Sponsor, the IRB, the DSMB, and regulators. Reporting by the site PI must be done in a timely manner. How quickly to report an event that has occurred depends on what the event is, how severe it is, and whether one or multiple Subjects was/were put at risk. Reporting should include what occurred as well as the response (corrective action) and how the deviation will be avoided in the future (preventive action).

6.13.2 Documentation of Huntington's Disease (HD)

Source documentation of a clinical diagnosis of symptomatic HD from Subject's medical provider will be required.

Confirmatory Genetic Testing. Most Subjects will have had genetic testing and report of a positive test (at least one allele with CAGn $\geq$37) can be expected in the documentation of HD to be provided by the Subject's clinician. Two tubes of blood will be obtained at randomization, one will be used for genetic testing and the other stored for future unspecified use. The results of the genetic testing will not be required for study entry. CAG genotyping will be performed for determination of the number of repeats for analysis (CAGn) of the data later. Results will be available to the biostatistical team for analysis of the influence of CAG length on the outcome variables. The second tube of blood will be stored and used for future unspecified use.

Dr. Marcy MacDonald's Laboratory at the Massachusetts General Hospital (Boston, MA) will conduct CAGn analyses. Results of any CAG testing will not be disclosed to the Subject unless a normal CAG repeat length is discovered for those individuals who previously had positive genetic testing, indicating misdiagnosis of HD. Should a CAG test result return as

normal, the test would be repeated and the site Investigator would be informed. If the normal test were confirmed, indicating misdiagnosis, the Subject would be informed by the site Investigator and withdrawn from further participation. Appropriate follow up (e.g., genetic counseling) would be recommended in the event of such a finding.

6.13.3 Protocol Amendments and Study Termination

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the CIRB. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the CIRB, except where necessary to eliminate an apparent immediate hazard to a study Subject.

The Sponsor and NeuroNEXT Network reserve the right to discontinue the study at a clinical study site(s) for safety or administrative reasons at any time. Should the study be terminated and/or the clinical study site closed for any reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative.

When changes occur in the conditions or procedures of a study that might affect individual Subjects, the Investigator should once again seek informed consent. Subjects who are enrolled in the study and actively participating in it should be informed of any changes and re-consented if these changes could affect their willingness to continue to participate. Adverse events may occur during a research study that could directly affect whether a prospective or enrolled Subject would wish to continue participating in it.

An enrolled Subject must sign a new consent form if the study has been significantly revised and/or includes the addition of risks to Subjects. The changes from the original consent form should be described to the Subject and Study Partner.

If consent has been obtained from a legally authorized representative and if the Subject regains the capacity to consent, he/she must be re-consented using standard procedures. If he/she refuses to do this, any data previously collected cannot be used for research purposes.

A determination of non-compliance by the IRB could result in a corrective action requiring re-consenting of Subjects before previously collected data can be used.

6.13.4 Assessments for Tolerability and Safety

6.13.4.1 Complete Medical History, Physical Examinations & Concomitant Medications

A complete medical history will be obtained at screening (by body system with current status) including lifestyle questions (i.e., tobacco use) will be obtained prior to randomization. A complete PE at screening, and exit, with a brief PE at baseline. Clinical evaluations at each subsequent in-person visit after randomization will review any changes since baseline and will involve clinical assessments including vital signs (blood pressures and heart rates), body temperature, and weight changes. All prescribed and over the counter medications, as well as and nutritional supplements will be documented.

6.13.4.2 Adverse Event (AE) Assessments

Adverse events, attribution of the adverse event to study drug, actions taken with respect to study drug (i.e., dosing changes), and classification of seriousness will be systematically documented. Serious adverse events (death, life-threatening adverse event, persistent or significant disability/incapacity, Subject hospitalization or prolongation of existing hospitalization or

congenital anomaly/birth defect) will be specifically noted and adjudicated for relationship to study drug.

6.13.4.3 Electrocardiogram (EKG)

A resting 12-lead electrocardiogram (EKG) will be completed at all in-person visits per the Schedule of Activities (APPENDIX A) for additional safety data and will consist of heart rate, PR, QRS interval, and QT and QTc. Site Investigators are responsible for review of EKG, ascribe clinical significance of any abnormalities and determine appropriate clinical follow-up.

6.13.4.4 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a suicidal ideation rating scale. It measures a Subject's degree of suicidal ideation on a scale ranging from wishing to be dead without an active plan to active suicidal ideation with a specific plan and intent to die.

6.13.5 Laboratory Evaluations

Blood and urine samples will be obtained for clinical safety lab assessments (complete metabolic panel, complete blood count, and urinalysis) at each in-person visit as described in the Schedule of Activities (APPENDIX A). A centralized clinical laboratory will manage laboratory specimens.

The following table lists the clinical safety lab tests that will be performed:

CLINICAL SAFETY LAB TESTS*		
METABOLIC PANEL	**COMPLETE BLOOD COUNT**	**URINALYSIS**
Sodium (Na)	White Blood Cell Count (WBC)	Color
Potassium (K)	Red Blood Cell Count (RBC)	Appearance
Chloride (Cl)	Hemoglobin (Hb)	Specific Gravity
Carbon Dioxide (CO2)	Hematocrit (HCT)	pH
Blood Urea Nitrogen (BUN)	Mean Corpuscular Volume (MCV)	Blood
Glucose	Mean Corpuscular Hemoglobin (MCH)	Glucose
Calcium (Ca)	Mean Corpuscular Hemoglobin Concentration (MCHC)	Protein
Creatinine (Crn)	Red Blood Cell Distribution Width (RDW)	Ketones
Bilirubin Total	Mean Platelet Volume (MPV)	Leukocyte Esterase
Albumin	Platelet Count (PLT)	Nitrite
Protein (NOS) Total		Urobilinogen
Glutamic-OxaloaceticTransferase (AST, SGOT)		Bilirubin
Glutamic-PyruvateTransferase (ALT, SGPT)		
Alkaline Phosphatase NOS		
Beta HCG (females only)		

*Additional tests may be conducted for safety assessments at planned or unscheduled visits as determined by the Investigator and/or IMM.

6.13.6 Exploratory Measures of SRX246 Activity

Irritability encompasses a range of behaviors that can be defined as reduced control over temper leading to negative verbal or behavioral outburst. A variety of instruments have been constructed to evaluate irritability and problem behaviors from the standpoint of the clinician, the Study Partner, or the Subject. Additionally, global clinical assessments are available and recognized for use to monitor the status of HD patients.

6.13.6.1 Aberrant Behavior Checklist (ABC)

The ABC scale was designed to measure treatment effects on mentally retarded Subjects with behavioral disturbances. It includes 15 irritability associated behavior items that constitute a subscale for irritability that will be administered to the Study Partner.

6.13.6.2 Problem Behaviors Assessment – Short Form (PBA-s)

The PBA-s is a structured interview in which the Investigator ascertains the frequency and severity of neuropsychiatric symptoms through observation and the reporting of the Subject and Study Partner. Assessed behaviors include depressed mood, suicidal ideation, anxiety, irritability, angry or aggressive behavior, apathy, perseverative thinking or behavior, obsessive-compulsive behaviors, delusional or paranoid thinking, hallucinations, and disoriented behavior.

6.13.6.3 Irritability Scale (IS)

The Irritability Scale (IS) is a 14-item self-administered questionnaire collecting information about different aspects of irritability utilizing a 0-3 scale for each item to indicate severity. The IS will be completed separately by Subjects and Study Partners (Chatterjee 2005).

6.13.6.4 Cohen-Mansfield Agitation Inventory (CMAI)

The CMAI is a 29-item list of aberrant behaviors that was designed to assess behavioral difficulties in institutionalized patients with dementia. The presence of these behaviors during the preceding 2 weeks will be identified and rated for frequency on a 1-7 scale by the Study Partner.

6.13.6.5 HD Clinical Assessments using the UHDRS '99 Rating Scale

Since 1993 the HSG has developed, tested, and refined a comprehensive clinical research instrument, the Unified Huntington's Disease Rating Scale '99 (UHDRS). The instrument assesses four major domains: motor function, cognitive function, behavioral abnormalities, and functional capacity. The scale was developed to be an efficient survey that is sensitive to different aspects of disease progression and to the disability or loss of function caused by HD. The HSG has established the inter-rater reliability and internal consistency of the scale (HSG 1996) and it has been used in all HSG clinical trials. Outcome variables derived from the UHDRS include the total motor score, total behavior frequency score, total behavior frequency x severity score, cognitive test scores (Symbol Digit Modalities Test, Verbal Fluency Test, Stroop Interference Test), Functional Checklist score, Independence Scale score, and Total Functional Capacity (TFC) score.

The disease-specific aspects of the UHDRS such as the total motor score are useful in understanding the variability in progression of HD and different disease phenotypes. The TFC is often considered the most clinically relevant component of the UHDRS because it focuses on key domains of function and uses simple scoring. It consists of five ordinal-scale items assessing a Subject's capacity in: occupation, financial affairs, domestic responsibilities, activities of daily living, and independent living. The sum of these items yields a TFC score that ranges from 0 (extreme incapacity) to 13 (full capacity). This score has been validated against radiographic measures of disease progression, including CT and MR measures of striatal volume and PET measures of striatal metabolism (Young 1986, Tabrizi 2012, Bamford 1989, Rosas 2008). The TFC shows a steady decline over the course of the illness and is especially sensitive to changes in the early and mid-stages of the disease (Marder 2000).

The UHDRS will be completed at designated visits as noted on the Schedule of Activities (APPENDIX A). The Motor and Behavioral subscales must be completed by the site Investigator. Qualified study staff may complete the Cognitive assessments if delegated by the site Investigator and designated on the Investigator, Study Staff and Related Duties Log.
Clinical Status and Quality of Life Assessments.

The Clinical Global Impression Scale (CGI), Caregiver Burden Assessment (CBA), and HD Quality of Life Scale (HD QoL) will measure the global impact of HD on the quality of life and general well-being of patients and their caregivers. The instruments are intended to supplement the measures of irritability and can be predicted to respond similarly, as they encompass the consequences of neuropsychiatric symptoms. Each has been used previously in

studies of HD patients. Additionally, the CGI has been used as a primary outcome measure in many conditions, including neurodegenerative and neuropsychiatric disorders, because it assesses the rater's impression of whether there is a response to a treatment. This study provides an opportunity to relate these global measures to performance to the irritability measures and the TFC.

The Clinical Global Impression (CGI) scales are frequently used as a primary or secondary outcome measure in psychiatric and cognitive disorders. This assessment must be completed by the site Investigator.

The Clinical Global Impression - Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of illness at the time of rating: 1, normal, not at all ill; 2, borderline ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

The Clinical Global Impression - Improvement scale (CGI-I) is a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

The Caregiver Burden Assessment (CBA) specifically for HD patients has recently been developed and validated (Chesire 2001) that was modified from the standard Caregiver Burden Interview instrument (Zarit 1986), an objective test for assessing subjective and objective caregiver burden in dementia patients. It was validated against the TFC, with which it is inversely correlated ($r = -.42$, $p < .05$), indicating increased levels of caregiver burden with progressive functional decline. It is also correlated with other UHDRS measures, such as the neuropsychological measures of cognitive dysfunction in the UHDRS suggesting a relationship between caregiver burden and cognitive disability. Understandably to those experienced with HD, there was no correlation with motor dysfunction. The CBA will be administered to the Subject's Study Partner, once consent has been obtained.

The HD Quality of Life (HD QoL) is a forty-question scale designed to be answered by the Subject, with input permitted from the Study Partner. The questions ask whether the quality of life has been impacted by various aspects of daily living that can become more difficult due to the expected symptoms of HD. The information is quantified using a 7 point estimation of frequency ranging from 'never' to 'all of the time'.

6.13.6.6 eDiary

A smart phone- or tablet-based eDiary will be prepared for use in this study. Subject- and Study Partner-specific questions will be provided, and both will be encouraged to use the eDiary two times a day. Using the eDiary, we hope to capture information about a Subject's general level of irritability/anger, time-of-day effects, anger triggers, etc. We also hope that the diary will improve dosing compliance and keep Subjects/Study Partners more engaged. This could contribute to improved retention. We will also use the eDiary to prompt Subjects to record the

time when they take their dose of drug (or placebo) the evening before they are scheduled for PK studies. We will remind them not to take drug (or placebo) on the morning of these studies.

6.13.7 Sparse Sampling Population PK of SRX246

Blood samples will be obtained periodically throughout the study for Sparse PK Sampling. Subjects will be prompted to note the time at which the dose of study compound is taken the night before in their eDiaries, and to bring their dose for the morning of the visit with them but not to take it until they are instructed to do so. Blood will be drawn as soon as the patient arrives in the clinic and the time of the blood draw will be recorded; then the morning dose of drug should be given and the time recorded. Two (2) hours later (time to be recorded), blood will be drawn again.

Objectives of the population pharmacokinetic analysis: 1) To characterize the population pharmacokinetics of SRX246 comparing sparse sampling data from Subjects with Huntington's Disease with detailed Phase 1 clinical trial pharmacokinetic assessments in healthy volunteers; and, 2) To identify patient-specific characteristics (e.g., age, gender, weight, disease severity) that may influence the PK parameter estimates of SRX246 in these populations.

Data to be included: 1) Individual SRX246 plasma concentrations from Study No. AVN005 (single-dose PK of 20, 40, 80, 160, and 320 mg oral doses in 33 healthy Subjects (Azevan Pharmaceuticals, Clinical Study Report for AVN005, Phase 1, Double-Blind, Placebo-Controlled, Ascending, Single-Dose, Safety, Tolerability, and Pharmacokinetic Study of SRX246 Capsules in Healthy Volunteers); 2) Individual SRX246 plasma concentrations from Study No. AVN007 (multiple-dose PK of 30, 60, 120 mg twice-daily doses given for 14 days in 18 healthy Subjects (Azevan Pharmaceuticals, Clinical Study Report for AVN007, Phase I, Double-Blind, Placebo-Controlled, Ascending, Multiple-Dose, Safety, Tolerability and Pharmacokinetic Study of SRX246 Capsules in Healthy Adult Volunteers.), and 3) Plasma concentrations of SRX246 obtained before (Cmin) and at approximately 2 hours (Cmax) after oral doses of 120 and 160 mg twice-daily given for at least 14 days in Subjects with Huntington's Disease. (N.B. The times at which SRX246 is taken the evenings before the Cmin determinations are made will be recorded by Subjects or their care givers. The times at which blood samples are drawn in the clinic the next morning will also be recorded. This, and the Cmax levels estimated by measuring SRX246 in the blood approximately 2 hours after Subjects take their morning dose of drug, will allow us to determine $t_{1/2}$ reasonably accurately.) Possible covariates to be evaluated include: body size, age, gender, and disease severity.

Data Input Format: The NONMEM data file requires Subject number, times of the doses, dose amounts, times of the plasma samples, plasma concentrations, values of covariates such as body size, age, etc. All data related to one patient, including dosage information, must be in chronological order. Data files will be constructed by use of automated data processing based on csv-files provided by the analytical company. At least 10% of the dataset will be checked manually.

Missing Data: For missing concentrations due to a concentration falling below the quantification limit of the bioanalytical assay the method of omitting these data points (Beal M1) and the Beal M3 method will be considered (Beal 2001).

Data Analysis Methods: Software: NONMEM version 7.3.0 (Icon Development Solutions, Ellicott City, MD). Self-written differential equations will be solved using the ADVAN6 PREDPP subroutine.

Model Diagnostics: Standard methods for diagnostics: The minimum value of the NONMEM objective function, typical goodness-of-fit diagnostic plots, and the evaluation of the precision of pharmacokinetic parameter and variability estimates will be used to discriminate between various models during the model-building process (Mould 2013).

Visual predictive checks: The model performance will be assessed by means of Visual Predictive Checks (VPC) (Bergstrand 2011). The VPC will be calculated based on 1000 datasets simulated with the final parameter estimates. The wide range of doses will require the use of prediction corrected VPC (pcVPC). These will be created by correcting the observed and simulated values for the average population prediction in the time-bin divided by population predictions for each observed and simulated value (Bergstrand 2011. The 10th, 50th and 90th percentiles will be used to summarize the data and VPC prediction. The pcVPC enables comparison of the confidence intervals obtained from prediction with the observed data over time. When the corresponding percentile from the observed data falls outside the 95% confidence interval derived from predictions, there is indication of some model misspecification.

Structural Model: The pharmacokinetic model found optimal in healthy volunteers will be employed. This is likely to be a two-compartment model for disposition of SRX246 and a transit-compartment input function to capture the absorption process (Savic 2007, Shen 2012).

Covariate Model: Possible relationships between patient specific covariates such as body size, age, gender, and disease severity and the individual pharmacokinetic parameter estimates will first be explored by graphical analysis. The individual estimates for eta (log-scale difference of the individual estimate from its population mean) of the respective pharmacokinetic parameters will be plotted against the individual values of the covariate (eta-plots). The effect of body size on the pharmacokinetic parameters will be predicated on allometric scaling. Other functions for covariate effects will be explored based on eta-plots. After accounting for body size, the potential effect of other covariates will be assessed. Covariates will be introduced into the model in a stepwise fashion. Inclusion of a specific covariate in the final model will be based on visual analysis of eta-plots, change in the NONMEM objective function, and the reduction in between-Subject variability (BSV). A clinically useful covariate will be expected to reduce the BSV in pharmacokinetic parameters by at least 10%.

Individual PK model: The between Subject variability (BSV) will be estimated for all parameters where feasible. An exponential parameter variability model or other appropriate parameter variability models will be considered for the PK parameters. Inclusion of between-occasion variability (BOV) will be considered.

Observation model: For the residual unidentified variability an additive, proportional, and a combined additive and proportional error model will be considered (Karlsson 1993).

6.13.8 Subject Adherence Assessments

At each study visit, the site Investigator and/or Study Coordinator will assess the Subject's compliance with the study requirements. This will include checks of protocol compliance, including use of study drug, concomitant medications, and eDiary data, if applicable in order to assess the reliability of Subject-generated data. (If applicable, note that Subjects who fail to comply with the study requirements may be withdrawn from the study.)

7 MANAGEMENT OF ADVERSE EXPERIENCES

The following types of events were reported in Subjects taking SRX246 in Phase I studies: tachycardia, conjunctival hyperemia, upper abdominal pain, diarrhea, epigastric discomfort, gastroesophageal reflux, lip pain, nausea, vomiting, chest pain. Almost all of these were mild in intensity, and they were not dose related. Thus, at this point, there are no expected adverse events or special precautions that need to be given to trial Subjects.

Section 10 below also includes a detailed description of AE definitions, assessment/ detection, grading (severity), potential relatedness to the investigational product, and reporting requirements. Below is a general strategy to guide modification or discontinuation of the study drug in response to AEs. The decision to decrease the dose of SRX246 or discontinue it altogether should be made by the site PI in consultation with the medical monitor should factor in potential relatedness of the AE to the study drug.

AE Grade	**Management**
≤ Grade 1 (mild)	No change in dose
Grade 2 (moderate)	*Hold until ≤ Grade 2. Resume at same dose level.
Grade 3 (severe)	*Hold until ≤ Grade 2. Resume at one dose level lower**
Grade 4 (life threatening or disabling)	Off protocol therapy

*Patients requiring a delay of > 1 week should go off therapy. Subjects can only hold medication once throughout the study. A Subject requiring a second hold should go off therapy.

**Patients requiring > two dose reductions should go off therapy.

Grade 1 AEs are defined as signs or symptoms that are easily tolerated. Grade 2 AEs are intense enough to interfere with usual activities. Grade 3 AEs interfere significantly with a Subject's ability to do work or his/her usual activities.

Worsening of Irritability and other Behavioral Symptoms

Since this study is expressly recruiting Subjects with irritability, which may coexist with anger, aggression, depression and suicidality, these symptoms represent expected adverse events due to the presence of HD, which will sometimes warrant intervention. Physicians who take care of HD and other movement disorder patients will have encountered these symptoms and will already be well versed in their management and in assessing the need for further assessment and intervention. Any Investigator who has completed a movement disorders fellowship will have had extensive training in management of suicidal ideation, worsening agitation and irritability, and other psychiatric symptoms in HD and other movement disorders. Training in the assessment and management of behavioral symptoms is provided to all HSG investigators at yearly HSG meetings as part of the Educational Program and will be included in the Investigator and Coordinator meetings. The site Investigator will be required to make a documented determination about whether clinical referral to a treating physician or acute intervention like hospitalization is warranted for AE s in this category that are grade 2 and above.

Investigators will be asked to characterize aggression AEs as:

1) Verbal aggression
2) Physical aggression: if physical: a) aggression toward self (self-injury, suicidal behavior); b) aggression toward others; c) aggression toward property; or d) aggression toward pets

Investigators will also be asked to report the outcome of these AEs:

1) Mental Health Referral
2) Emergency Room Visit
3) Psychiatric Hospitalization
4) Concomitant medications added

As part of the site initiation visit, sites will be given a worksheet to complete to document their local procedures for:

1) Escorting a patient from a study visit to the Emergency Room if needed due to exacerbation of behavioral symptoms
2) Setting up a rapid mental health referral (including names and contact for local psychiatrists, psychologists)
3) Facilitating a psychiatric hospitalization (contact names and numbers for local units with which they have a relationship)
4) Dealing with emergency phone call from Subject or care partner for worsening of behavioral symptoms

An Independent Medical Monitor (IMM) may also review all AEs, in a blinded fashion, on a periodic basis. In addition, the IMM will review all events that meet the regulatory definition of a Serious Adverse Event upon receipt of notification via the Electronic Data Capture (EDC) system.

Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies that occur during paternal or maternal exposure to study drug (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be determined and documented even after the Subject has been withdrawn from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. Pregnancy and all outcomes of pregnancy must be reported to the Coordination Center.

8 GENERAL DESIGN ISSUES

The study design consists of three parallel arms: placebo and two final doses of SRX246 (120 mg BID and 160 mg BID). Thirty-six patients will be randomized into each study arm. Since we have only given SRX246 to generally healthy subjects thus far, and since some HD patients may be frailer population, we have elected to initiate treatment at 80 mg BID; to increase the dose of drug to 120 mg BID after two weeks in those patients who have tolerated the starting dose; and to increase the dose of drug again after 2 additional weeks in those patients who are taking 160 mg BID. Subjects in the placebo group will take capsules that will be identical in appearance to those containing SRX246. Thus, patients and study staff will both be blind to treatment, and twice as many Subjects will receive active agent as placebo. The placebo group will be used for comparison with each active drug group.

Subjects who are unable to increase their dose of drug can remain in the study at the highest dose they can tolerate, and Subjects who find the drug intolerable can reduce the dose of drug (to 80 mg BID of SRX246 or placebo, but no lower without dropping out of the study). The goal is to study the behavioral scales in as many people as possible because we feel that this will be important to the clinical research community.

At the end of the trial, data from all Subjects who were given placebo will be combined, and two pairwise tests will be performed (120 mg vs placebo, 160 mg vs placebo--see below).

It may be necessary to screen as many as 150 candidates to enroll 108 Subjects. Up to 20 NeuroNEXT sites may participate in the study, with each site's goal to enroll about 5-6 Subjects within the first 18 months of the trial.

8.1 Outcomes

8.1.1 Primary Outcome: Tolerability

The primary endpoint will be tolerability, defined as the proportion (percentage) of completers. Each treatment group will be compared to the control group, and the statistical test of equivalence of tolerability will involve two pairwise tests (120mg vs placebo, 160mg vs placebo).

8.1.2 Secondary Outcome: Safety

The secondary aim of the analysis is safety, with the endpoint defined as the proportion of participants who experience an adverse event. An equivalence analysis for safety will be performed, similar to that discussed for tolerability.

8.1.3 Exploratory Aim: Activity

The exploratory aim is to examine several measures of irritability and other problem behaviors, and clinical assessments for activity signal. The following measures will be compared to each other in order to examine relative effect sizes. The endpoint will be rate of change (slope) over 12 weeks.

Unified Huntington Disease Rating Scale (UHDRS)
Clinical Global Impression (Severity, CGI-S and Improvement, CGI-I)
Aberrant Behavior Checklist (ABC), irritability subscale

Cohen-Mansfield Aggression Inventory (CMAI)
Problem Behaviors Assessment – short form (PBA-s)
Irritability Scale (IS)
HD QoL
Caregiver Burden Questionnaire

8.2 Sample Size and Accrual

Primary Aim: Analysis and Sample Size. The study design consists of three parallel arms: placebo and two final doses of SRX246 (120mgBID, 160mgBID). The primary endpoint will be tolerability, defined as the proportion (percentage) of completers. Each treatment group will be compared to the control group, and the statistical test of tolerability will involve two pairwise tests (120 mg vs placebo, 160 mg vs placebo). Our immediate focus will be on a single test using an alpha-correction for multiple comparisons.

The Go/No Go decision for further consideration of SRX246 will be based on testing tolerance among the placebo (P) and treatment (T) groups using a single-tailed test. Because equality of tolerance is consistent with the Go decision, there is perhaps a temptation to under-power a study using the traditional test of the null hypothesis of equal group population proportions. Setting a low sample size will make it difficult to reject the null and perhaps provide an unfair or unrealistic test of equal tolerability. As an alternative, we propose a test of non-inferiority (Blackwelder 1982) that powers for the rejection of the null hypothesis that the population proportion difference is greater than or equal to a margin value, δ. Suppose π_T is the proportion of completers for the T group and π_P is the same for the P group. The null hypothesis and alternative hypothesis of non-inferiority are respectively, H_0: $\pi_P - \pi_T \geq \delta$, H_A: $\pi_P - \pi_T < \delta$, so that under H_A, $\pi_T > \pi_P - \delta$ (the T completer proportion is greater than the P proportion adjusting for the margin).Equivalence of tolerability within the margin is consistent with the rejection of the null hypothesis and will constitute a Go decision for further consideration of SRX246, perhaps in a Phase IIb study to detect signs of activity. Conversely, failure to reject the null hypothesis will result in a No Go decision.

The advantage of the non-inferiority approach is that sample size planning can be based on the power to reject the null hypothesis, which is consistent with traditional approaches. If the sample size is large, H_0 can be evaluated using an asymptotic single-tailed test, with z-value

$$z = \frac{\hat{\pi}_P - \hat{\pi}_T - \delta}{\sqrt{\frac{\hat{\pi}_P(1-\hat{\pi}_P)}{n_P} + \frac{\hat{\pi}_T(1-\hat{\pi}_T)}{n_T}}}$$

where n_P is the sample size for the P group, and total sample size is $N = 3n_P$.

The above equation indicates that a power analysis for planned sample size requires candidate values for π_P, π_T and δ, for fixed type 1 error rate (α) and type 2 error rate (β). Following the practice of the Huntington Study Group (HSG 1998; 2003; 2004; 2009), the margin was set at $\delta = 0.50$ for all analyses, though a follow-up margin sensitivity analysis was performed (see below). A difference of 50% between P and T is considered acceptable because of the paucity of effective treatments for HD (HSG 1998). For the remaining parameters, plausible values were based on published literature for randomized clinical trials (RCTs) in HD.

Table 4 below shows completer information for P and T groups of six HD RCTs employing various drugs.

Table 4. Tolerability information from HD clinical trials.

			Completer Percentage		
Study	Drug	N	Placebo	Treatment	Difference
HSG (2009)	Tetrabenazine	84	97%	91%	6%
Kieburtz (2010)	Latrepirdine	91	82%	87%	5%
HSG (1998)	OPC-14117	64	94%	81%[a]	13%
HSG (2003)	Riluzole	63	91%	87%[a]	4%
HSG (2004)	Minocycline	60	96%	78%[a]	18%
Squitieri (2013)	Pridopidine	353	86%	86%[a]	0%

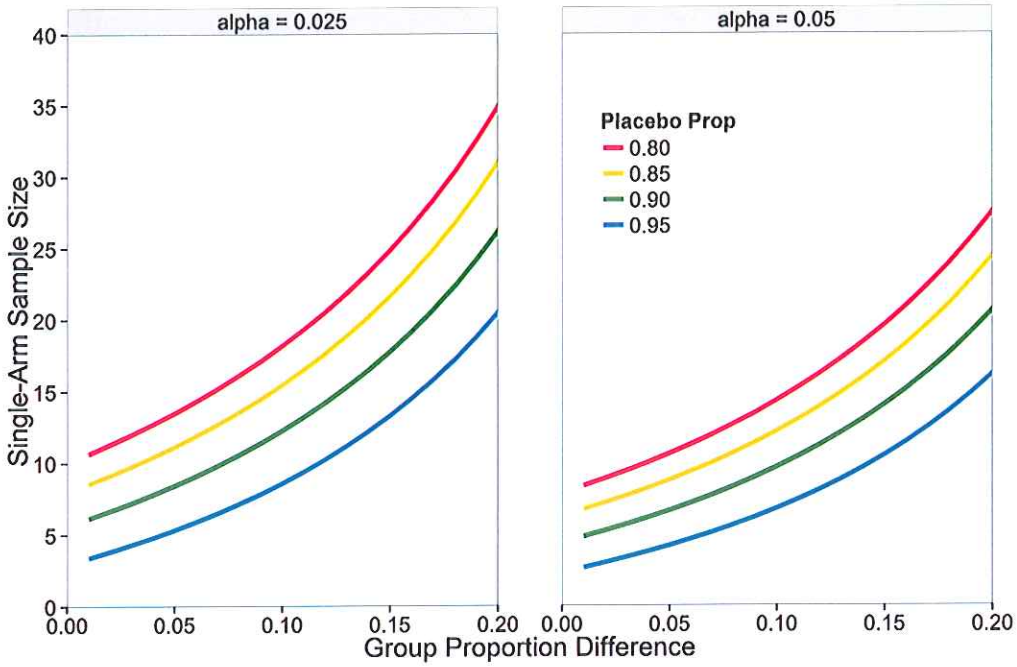
Note. [a]Percentage is the minimum among multiple treatment arms.

Placebo completion rate ranged from 82%-97% and the group difference ranged from 0%-18%. In light of the information in Table 4, sample size was computed for

$\pi_P = 0.80, 0.85, 0.90, 0.95$ and $\pi_P - \pi_T = 0.01, 0.02, \ldots, 0.19, 0.20$. It should be noted that the minimum $\pi_P = 0.80$ is less than any placebo value in Table 4, and the maximum $\pi_P - \pi_T = 0.20$ is greater than any difference in Table 4, so these values constitute reasonable bounds for selecting required sample size. The non-inferiority test is single-tailed, and the type I error rates of $\alpha = .05 / 2 = .025$, and $\alpha = .10 / 2 = .05$ were used to allow for two comparisons (each dose level versus placebo), with power set at 80% ($\beta = 0.20$).

The results of the power analysis are shown in Figure 4 below. The Figure shows the single-arm sample size (n_P) as a function of the P group proportion (π_P), and the group proportion difference ($\pi_P - \pi_T$) paneled by α-level. As discussed, the combination of $\pi_P - \pi_T = 0.20$ and $\pi_P = 0.80$ appear to be reasonable bounds for sample size selection. In the left-hand panel, the upper red line shows that conducting two tests each at $\alpha = .025$ and 80% power requires approximately 35 participants per group for the smallest proposed control proportion ($\pi_P = 0.80$) and the largest proportion difference ($\pi_P - \pi_T = 0.20$). Therefore, we propose a total sample size of $N = 3n_P = 105$.

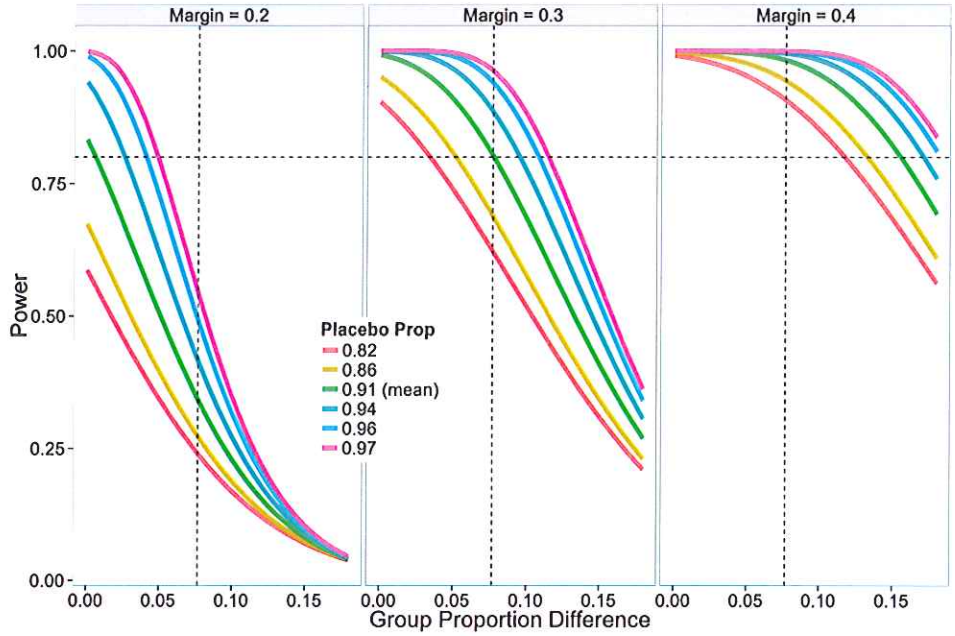
Figure 4. Sample size for the placebo group as a function of effect size, placebo proportion, and alpha-level (80% power).



Further Sample Size Considerations. The power analysis suggests that a total sample size of $2n_P = 70$ will be used for each comparison of completer proportions (120mg vs placebo, 160mg vs placebo). The margin used to derive this sample size, $\delta = 0.50$, allows the possibility of a relatively small proportion of completers in the T group. For example, if $\pi_P = 0.90$, H_0 will be rejected if $\pi_P > 0.40$, meaning there could be a minority of completers. In order to assess the sensitivity of the sample size to a change in margin value, we examined the power of the z-test for the observed values in Table 4 with $n_P = n_T = 35$ fixed for all calculations, and $\alpha = 0.025$ to allow for two comparisons. Figure 5 shows power as a function of the Table 4 P group proportions, group proportion differences, and various margin values. The vertical dashed line indicates the mean group difference of 0.08 (mean P proportion is 0.91), and 80% power is indicated by a horizontal dashed line. Using the mean Table 4 values as a reference, the middle panel indicates that with the selected sample size the margin can be decreased to 0.30 and still provide 80% power to reject H_0 (the point defined by the intersection of the dashed lines). Assuming the mean values of Table 4, the 0.30 margin allows for rejection of H_0 for $\pi_T > 0.61$. If the proportions of the proposed study are equal to the mean values of Table 4, then the statistical power will be high enough to reject H_0 for a margin as low as 0.30 with a majority of completers in the T group. We also note that the left-most panel of Figure 5 shows that an even lower margin (e.g., $\delta = 0.20$) will provide adequate power if the P and T proportions are relatively close to 1 and approximately equal (close to no difference).

Figure 5. Power for $n = 35$ per group as a function of Table 4 placebo group proportion, group proportion difference (placebo minus treatment), and margin value.

The dashed horizontal line indicates the conventional 80% power value and the vertical dashed line indicates the average Table 4 group difference.



An additional consideration is that using the asymptotic test with our estimated sample size might not be optimal. The asymptotic test can be inaccurate with smaller sample sizes, especially when π_P (or π_T) is close to 1, as is anticipated in the proposed study (cf Table 4) (Fagerland 2011). Computer-intensive exact methods can have better performance under these conditions (Santner 2007). The exact method discussed by Wang (2010) will be used for the proposed analysis of tolerability and safety (the latter is discussed below). Wang's method appears to have superior performance to other approaches, and software is readily available (Wang 2013).

Secondary Aim: Safety. The secondary aim of the analysis is safety, with the endpoint defined as the proportion of participants who experience an adverse event (AE). A non-inferiority analysis for safety will be performed, similar to that discussed for tolerability. Primary focus will be on the comparison of 160mg vs placebo. H_0 for non-inferiority will be evaluated using the methods previously described with the same margin of difference, $\delta = 0.50$.

Consistent with the recent JAMA Guide to Statistics and Medicine (Detry 2014) the analysis will be performed consistent with the intent-to-treat principle, meaning an attempt will be made to analyze all enrolled patients. Missing data methods, such as imputation, might be used to handle dropout (note this is not an issue for the tolerability analysis as the proportion of completers is the endpoint).

Exploratory Aim: Activity of Measures. The exploratory aim is to examine several measures of irritability and other problem behaviors and clinical assessment for activity signal. Measures will be compared to each other and also compared to clinical assessments in order to examine relative

effect sizes. The endpoint will be rate of change (slope) over 12 weeks. Linear mixed models (LMMs) (Verbeke 2000) will be used to examine slope differences among the placebo and treatment groups. LMMs are appropriate for the analysis because they account for dependency due to repeated measures and can be estimated with maximum likelihood (ML) procedures.

Consistent with the intent-to-treat principle, ML estimation can accommodate missing data under the assumption that the missing data mechanism is ignorable (Little 1987). Suppose Y_{ij} is the irritability score for the ith patient ($i = 1, \ldots, N$) at the jth week ($j = 1, \ldots, n_i$), and t_{ij} denotes time in weeks. Assuming linear change over time, the LMM can be written as the following,

$$Y_{ij} = \alpha + \beta t_{ij} + \gamma t_{ij} g_{120i} + \delta t_{ij} g_{160i} + (a_i + b_i t_{ij} + \epsilon_{ij})$$

where g_{120i} is a dummy variable for the 120mg group membership (1 = in the group, 0 = otherwise), and g_{160i} is a dummy variable for the 160mg group. In the equation, α is the intercept (baseline level) that is common among groups due to random assignment; β is the slope for the placebo group; γ is the 120mg vs placebo slope difference; and δ is the 160mg vs placebo slope difference. The terms a_i and b_i are the random effects (random intercepts and slopes, respectively), and ϵ_{ij} is random error. We make the typical assumptions, $[a_i \quad b_i]^T \sim \mathcal{N}(\mathbf{0}, \boldsymbol{G})$, $\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2 \boldsymbol{I}_i)$, and $[a_i \quad b_i]^T \perp \epsilon_{ij}$.

An evaluation of the null hypothesis that the slopes are equal among the groups can be performed with the likelihood ratio test (LRT). The LRT is based on a comparison of the full model above and a reduced model omitting $\gamma t_{ij} g_{120i} + \delta t_{ij} g_{160i}$. Alternatively, a global effect size can be computed as the difference of Akaike's information criterion (AIC) for the full and reduced model (Burnham 2002). The statistical strategy is to estimate the full and reduced model for each irritability and clinical variable separately. Then the difference in AIC for each variable (full vs reduced model) can be used to assess relative strength of effect in discriminating among the groups. Because larger AIC differences indicate larger effect sizes (i.e., greater discrimination), the variable with the largest AIC difference (or the top few variables) will be a candidate for further study in clinical trials of efficacy. AIC differences of the irritability variables relative to the clinical variables will provide a context for judging the effect size of the former compared to general motor, cognitive, and functional variables in HD. The difference in AIC has been found to be a useful method of screening candidate variables for efficacy in HD research (Leoni 2013, Paulsen 2013).

9 DATA AND SAFETY MONITORING, COLLECTION AND MANAGMENT

9.1 Data Management

Data Management (DM) is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with NeuroNEXT policies, and applicable Sponsor and regulatory requirements. The DCC is responsible establishing procedures to ensure that all aspects of clinical data management activities occur as required, and for properly instructing site personnel to collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data.

Site personnel will collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The DCC is responsible for developing, testing, and managing clinical data management activities. The DCC will monitor clinical sites to ensure compliance with data management requirements and Good Clinical Practices.

9.2 Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical study site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. NeuroNEXT CIRB approval for the protocol must be on file at the DCC before accrual can occur from the clinical study site.

The DCC will use a system of coded identifiers to protect participant confidentiality. When the participant is registered to participate in the study using the DCC-provided web-based registration, the system will assign a participant ID number. The unique ID code will include a protocol ID, a site ID, and a unique participant ID. To confirm the correct participant ID, the data entry system will require a second entry of the unique participant ID and compare for consistency. In this fashion, no personal identifiers would be accessible to the DCC and the data will be collected on the correctly identified Subject.

9.3 Data Entry

The general NINDS Common Data Elements (CDE) will be used to construct many of the data collection forms. All study data will be collected via systems created in collaboration with the DCC and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

Data entry will occur at the enrolling clinical study sites. Data quality assurance and analyses will be performed by the DCC. The DCC, located at the University of Iowa, will coordinate all data and statistical services for the study, as well as on-site monitoring for all participating clinical study sites.

Data collection for this study will be accomplished with online electronic case report forms. Using encrypted communication links, online forms will be developed that contain the requisite data fields.

9.4 Quality Assurance

By signing this protocol, the Sponsor and Investigator agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

9.5 Development of Monitoring Plan

Onsite monitoring visits will be conducted by DCC monitors according to a pre-defined Monitoring Plan. The monitoring plan will detail the frequency of on-site visits, the study data to be monitored, the review of any regulatory files, drug and supplies accountability (if applicable), documentation of the on-site visit, and the resolution process for data errors that are discovered during the visits. All participating clinical study sites will be monitored at least once after a study initiation visit and all sites will have a close-out visit for each protocol. One on-site monitoring visit is anticipated for each clinical study site per year. All Subjects will be monitored for inclusion and exclusion criteria, informed consent procedures, and adverse events. A certain percentage of data is also monitored/ source data verified against the data entered into the study database. The monitoring plan will include flexibility to revise the frequency of visits or data monitored depending on clinical study site or study related issues.

9.6 Site Monitoring Visits

All aspects of the study will be monitored by qualified individuals. Monitoring will be conducted according to Good Clinical Practice (GCP) and applicable government regulations. The Investigator agrees to allow monitors access to the clinical supplies, dispensing and storage areas, and to the clinical files of the study Subjects, and, if requested, agrees to assist the monitors.

On-site monitoring visits will be conducted by DCC monitors according to a pre-defined monitoring plan for each protocol. The goal of on-site monitoring is to analyze (review) the data as it is collected, to check the validity and integrity of the data, to verify source documentation, to ensure protection of human Subjects, and to ensure protocol compliance with federal regulations. During the monitoring visit, the monitor assesses the overall status of the study, staff, and facilities to determine whether the study is being conducted per protocol and in compliance with regulatory requirements. The monitor also conducts a CRF review that includes checks of all adverse event documentation, verifies the presence of all critical correspondence and records related to investigational products and clinical supplies (if applicable), and determines if protocol violations have occurred and are documented properly.

After the monitoring visit, the monitor documents the results of the monitoring visit and completes a post-visit monitoring letter that conveys any issues discovered during the visit and the need for data corrections, if appropriate. Drug and supplies accountability may also be monitored during the site visit. The DCC will work closely with the CCC to monitor and document drug distribution from the manufacturers to the clinical study sites (CSS). Each CSS will be provided with a drug accountability log which will be reviewed by the DCC monitors and reconciled with distribution logs. At study closeout the DCC and CCC will confirm that appropriate data have been reviewed, source documentation has been verified, and all required documents are present in the Study Regulatory File.

9.7 Laboratory Data Flow

The DCC will provide laboratories with online forms and/or electronic data exchange mechanisms - depending on their capabilities and needs - to enter, update and obtain relevant data. When a blood or urine sample has been obtained, the clinical study site study Coordinator will send the sample (participant ID, site ID, and protocol ID numbers will be used) to the University of Rochester central laboratory. Results will be sent via a secure system to University of Rochester laboratory with no individual-identifying information on the report. The laboratory will electronically communicate the test results to the respective clinical study sites in a secure manner. The laboratory will also transfer test results electronically to the DCC.

9.8 Safety Monitoring

Safety monitoring will include careful assessment and appropriate reporting of adverse events (AEs). Medical monitoring will include contemporaneous assessment of serious adverse events. Refer to Section 10 for AE definitions and additional information.

The monitoring of Subject safety and data quality will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. A Data and Safety Monitoring Board (DSMB) appointed by the NIH/NINDS will meet at six-month intervals (or as determined by the NINDS) to review partially unblinded study data provided by the study statistician. This committee will monitor rates of adverse events and endpoints in the trial and will monitor the performance of the trial. The frequency and format of DSMB meetings, reports, and guidelines will be agreed upon prior to study Subject enrollment.

An Independent Medical Monitor (IMM) will be appointed to review all adverse events, in a blinded fashion, on a periodic basis. In addition, the IMM will review all events that meet the regulatory definition of a Serious Adverse Event, upon receipt of notification via the Electronic Data Capture (EDC) system.

FDA, Office of Human Research Protection (OHRP), and NeuroNEXT CIRB requirements for reporting AEs will be followed. Subjects will be monitored for AEs from the time they are randomized until 30 days following permanent discontinuation of study drug. At that point, all ongoing AEs will be followed to resolution or stabilization, whichever occurs first, but no new AEs will be recorded. The IMM/DSMB will review cumulative AEs; the frequency of this review will be determined by the IMM/DSMB.

For the purposes of this study, before randomization, only those adverse events, serious and non-serious, that in the opinion of the Investigator are deemed related to study procedures will be reported. After randomization, all adverse events will be reported.

Each Clinical Study Site Principal Investigator and research team (co-investigators, research nurse, clinical trial coordinator) are responsible for identifying and reporting AEs and determining the relationship of the event to the study drug/study procedures. Aggregate reports blinded by treatment group, detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures, will be prepared by the DCC. A separate report detailing protocol compliance will also be available monthly from the DCC. A determination will be made as to whether the protocol or informed consent document requires revision based on these reports.

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and International Conference on Harmonization (ICH) guidelines. The site Investigator will carefully monitor each Subject throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Each clinical study site's Principal Investigator and research team are responsible for identifying adverse events and reporting them through the DCC Online Adverse Event Reporting System. Investigators are also responsible for complying with NeuroNEXT CIRB's reporting requirements for all safety reports. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

10 DEFINITIONS OF ADVERSE EVENTS, SUSPECTED ADVERSE DRUG REACTIONS & SERIOUS ADVERSE EVENTS

10.1 Adverse Event and Suspected Adverse Drug Reactions

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

Clinical → symptoms reported by the Subject or signs detected on examination.

Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures: the results of which are not being captured as AEs).

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the site Investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the site Investigator.

Expected adverse events are those that are known to be associated with or have the potential to arise as a consequence of participation in the study. As noted earlier, the following problems were reported in Subjects taking SRX246 in Phase I studies: tachycardia, conjunctival hyperemia, upper abdominal pain, diarrhea, epigastric discomfort, gastroesophageal reflux, lip pain, nausea, vomiting, chest pain. Almost all of these were mild in intensity. The problems were not dose related.

Unexpected adverse events are those adverse events, the specificity or severity of which are not consistent with the current Investigators Brochure or package insert or described in the protocol. An unexpected, suspected adverse drug reaction is any unexpected adverse event that, in the opinion of the site Investigator or Sponsor, there is a reasonable possibility that the investigational product caused the event.

10.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study Subject, in the view of the site Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled "procedure" or a "treatment" is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the Subject's ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the Subject (whether the Subject is male or female).
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience, and will therefore, not be considered an SAE. An example of this would include a social admission (Subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE that, in the opinion of the site Investigator or Sponsor, suggests a reasonable possibility that the investigational product caused the event.

The site Investigator is responsible for classifying adverse events as serious or non-serious.

10.3 Assessment and Recording of Adverse Events

This study will utilize the CTCAE version 4.0 coding system for adverse event recording. Adverse events reported using CTCAE will be recoded into MedDRA terms by the DCC.

10.3.1 Assessment of Adverse Events

At each visit (including telephone interviews), the Subject will be asked "Have you had any problems or symptoms since your last visit?" in order to determine the occurrence of adverse events. If the Subject reports an adverse event, the Investigator will determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

10.3.2 Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the site Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.
3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the Subject's clinical state or by other modes of therapy administered to the Subject. (suspected ADR)

4. Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the Subject's clinical state. (suspected ADR)
5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (suspected ADR)

10.3.3 Recording of Adverse Events

All clinical adverse events are recorded in the Adverse Event (AE) Log in the Subject's study binder. The site should fill out the AE Log and enter the AE information into the online Adverse Event Reporting System within 5 working days of the site learning of a new AE or receiving an update on an existing AE.

Please Note: Serious Adverse Events (SAEs) must be reported to the NeuroNEXT Data Coordinating Center within 24 hours of the site learning of the SAE.

Entries on the AE Log (and into the online Adverse Event Reporting System) will include the following: AE term(s) and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

10.3.4 Adverse Events and Serious Adverse Events - Reportable Events

The following are considered reportable events and must be reported to the NeuroNEXT Data Coordinating Center within 24 hours of the site being notified of the event.

- All events that meet the above criteria for Serious Adverse Events (SAEs)

All occurrences of Serious Adverse Events (SAEs) must be reported within 24 hours of discovery of the event. All other Adverse Events (AEs) must be reported within 5 working days/7 calendar days of discovery of the event.

The following will be considered reportable events and will be reported to the coordination center within 24 hours of the event, or the site Investigator's knowledge of the event:

Dosage suspension
Dosage reduction
Dosage rechallenge
Subject withdrawal
Early discontinuation of study drug
Serious adverse event
Suicide attempt
Emergency treatment disclosure
Clinically significant overdosage of study drug
Pregnancy

10.3.5 On-line Adverse Event Reporting System

Upon entry of a serious adverse event by a site Investigator, the DCC Online Adverse Event Reporting System will immediately notify the Independent Medical Monitor (IMM).

- Within **24 hours** (of learning of the event), investigators must report any Serious Adverse Event (SAE).
- Investigators must report all other AEs within **5 working days/7 calendar days** (of learning of the event).

Serious adverse events: The site Investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM will review the SAE report. The IMM may request further information if necessary. The Online Adverse Event Reporting System maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study. The IMM may determine that the Serious Adverse Event requires expedited reporting to the FDA. The DCC will prepare a Medwatch safety report for submission to the FDA. If warranted, the IMM will notify the DSMB chair. The DSMB may suggest changes to the protocol or consent form to the Study Chair as a consequence of adverse events.

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the Investigator or a member of his research team will be submitted to the DCC in a timely fashion (within 5 working days). The events will be presented in tabular form and given to the IMM on a quarterly basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DCC will prepare aggregate reports of all adverse events (serious/not serious, expected/unexpected and relationship to study drug) for the IMM and the DSMB on a quarterly basis or as requested. In addition, all adverse events will be coded using the MedDRA system. A separate report detailing protocol compliance will also be available from the DCC for DSMB and/or site review monthly or as requested. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

10.3.6 Adverse Event Data Management System (AEDAMS)

Upon entry of a serious adverse event by a clinical site, the DCC Online Adverse Event Reporting System will immediately notify the IMM. If warranted, the IMM will notify the DSMB chair. The DCC will prepare aggregate reports of all adverse events (serious/not serious and expected, unexpected) for the DSMB.

11 HUMAN SUBJECTS

Documented approval from the NeuroNEXT CIRB will be obtained for all participating centers prior to clinical trial start, according to ICH GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the CIRB approval must be obtained.

Evidence of training in responsible conduct of research shall be on file for each CSS PI and co-investigator.

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the NeuroNEXT CIRB responsible for oversight of the study. A signed consent form, approved by the NeuroNEXT CIRB, will be obtained from the Subject. For Subjects who cannot provide consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the Subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the Subject, parent, or legal guardian, and this fact will be documented in the Subject's record.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the clinical study site will be identified only by the study specific Subject Identification Number (SID) to maintain Subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using study specific SIDs only. Clinical information will not be released without written permission of the Subject, except as necessary for monitoring by CIRB, the FDA, the NINDS, the OHRP, the Sponsor, or the Sponsor's designee.

11.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the CIRB, the NINDS, the Sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research Subjects are protected.

12 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies of the NeuroNEXT Network and procedures developed by the NeuroNEXT Data Sharing and Publication Committee. Any presentation, abstract, or manuscript will be made available for review by the Sponsor and the NINDS prior to submission.

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APPENDIX A: Schedule of Activities and Study Procedures

Week	SC	BL	2	4	6	8	10	12	F/U
Visit Window	Day -30 to 0	Day 0	Day 14±5	Day 28±5	Day 42±5	Day 56±5	Day 70±5	Day 84±5	Day 91±5
Visit	SC	BL	01	T1	02	03	04	05	T2
Assessment / **Dosing (BID)**	none	80 mg	120 mg		120 or 160mg				none
Informed Consent (Subject)	X	R							
Informed Consent (Study Partner)	X	R[a]	R[e]	R[e]	R[e]	R[e]	R[e]	R[e]	
Assign Subject ID / Unique Site ID number	X								
Inclusion/Exclusion Criteria	X	R							
Screening Demographics (Subject)	X								
Screening Demographics (Study Partner)	X	R[a]	R[e]	R[e]	R[e]	R[e]	R[e]	R[e]	
Medical & Surgical History	X								
Review methods of birth control with men and women	X	X							
Complete Physical Exam, including neurological	X							X	
Height, Weight (wt)	X				X(wt)			X(wt)	
Orthostatic Vital Signs (HR, BP), and Body Temperature	X	X[b]	X		X	X[b]	X	X	
Resting 12-Lead EKG	X	X	X		X	X	X	X	
Safety Labs (Hematology, Chemistry, Urinalysis)	X		X		X	X	X	X	
Pregnancy Test (females only)	X(s)	X(u)			X (s)			X(s)	
Urine Drug Screen	X								
Blood Collections for CAGn Genotyping and storage		X	R[f]		R[f]	R[f]	R[f]	R[f]	
Randomization Assignment		X							
Dispense Study drug		X	X		X	X	X		
Instruct Subject and Study Partner about Study Drug		X	X		X	X	X	X[c]	
Administer Study Drug on Site		X				X	(X)[d]		
Sparse PK Blood Collections						X	(X)[d]		
Review Study Drug Compliance			X	X	X	X	X	X	

Week	SC	BL	2	4	6	8	10	12	F/U
Visit Window	Day -30 to 0	Day 0	Day 14±5	Day 28±5	Day 42±5	Day 56±5	Day 70±5	Day 84±5	Day 91±5
Visit	SC	BL	01	T1	02	03	04	05	T2
Assessment / **Dosing (BID)**	none	80 mg	120 mg		120 or 160mg				none
Assessments for Adverse Events		X	X	X	X	X	X	X	X
Assessments for Concomitant Medication Use		X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (CSSRS)	X	X	X		X	X	X	X	
Unified Huntington Disease Rating Scale (UHDRS)	X	X			X			X	
Clinical Global Impression – Severity of Illness (CGI-S)		X							
Clinical Global Impression – Improvement (CGI-I)					X			X	
Provide eDiary and Instructions		X	R	R	R	R	R	R	
Aberrant Behavior Checklist (ABC), irritability subscale		X			X			X	
Cohen-Mansfield Aggression Inventory (CMAI)		X			X			X	
Problem Behaviors Assessment – short form (PBA-s)		X			X			X	
Irritability Scale (IS)		X			X			X	
HD QoL		X			X			X	
Caregiver Burden Questionnaire		X			X			X	
Participant/Study Partner/PI Blindedness Questionnaire								X	

a – If not performed at screening.
b – Conduct pre-dosing and 1-2 hours post first dose of administering study medication.
c – Return all study drug supplies to clinic, do not issue additional study drug
d - If not performed during Week 8, perform at Week 10.
e – Review and re-administer if study partner changes
f – If two tubes not collected at BL, ensure two tubes are collected by Week 12 (Visit 05)
R –Review; (s) – Serum test; (u) – Urine test
Definitions for Study Weeks/Visits: SC – Screening; BL – Baseline; T – Telephone Contact; F/U – Follow-up