

Clinical Study Protocol with Amendment 3

**An Open-Label, Long Term Safety Study of SD-809 ER in Subjects with Chorea
Associated with Huntington Disease**

Study SD-809-C-16

NCT01897896

Protocol with Amendment 3 Approval Date: 2 March 2015



CONFIDENTIAL

**The following contains confidential, proprietary information, which is the property of
Auspex Pharmaceuticals, Inc.**

PROTOCOL NUMBER: SD-809-C-16

**AN OPEN-LABEL, LONG TERM SAFETY STUDY OF SD-809 ER IN
SUBJECTS WITH CHOREA ASSOCIATED WITH
HUNTINGTON DISEASE**

Alternatives for Reducing Chorea in Huntington Disease (ARC-HD)

02 March 2015

Amendment 3

Development Phase: 3

STUDY CONTACTS

SPONSOR:	Auspex Pharmaceuticals, Inc. 3333 N. Torrey Pines Court, Suite 400 La Jolla, CA 92037 USA [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
Principal Investigator	[REDACTED] [REDACTED] [REDACTED]
Co-Principal Investigator	[REDACTED] [REDACTED] [REDACTED]
CLINICAL MONITOR	[REDACTED] [REDACTED] [REDACTED]

PROTOCOL SYNOPSIS

PROTOCOL	SD-809-C-16
TITLE	An Open-Label, Long Term Safety Study of SD-809 ER in Subjects With Chorea Associated With Huntington Disease
Running Title	Alternatives for Reducing Chorea in HD (ARC-HD)
PHASE	3 (Safety)
INDICATION	Treatment of chorea associated with Huntington disease
NO. SITES	Approximately 40
OBJECTIVES	<ol style="list-style-type: none"> 1) Evaluate the safety and tolerability of titration and maintenance therapy with SD-809 ER 2) Evaluate the safety and tolerability of switching subjects from tetrabenazine to SD-809 ER 3) Evaluate the pharmacokinetics of tetrabenazine, SD-809 and their respective α- and β-HTBZ metabolites in subjects switching from tetrabenazine to SD-809 ER
STUDY POPULATION	Approximately 116 male and female adult subjects with manifest Huntington disease (HD) who are receiving approved doses of tetrabenazine for treatment of chorea (approx. 36) or have successfully completed the SD-809-C-15 efficacy study (approx. 80) will be enrolled.
STUDY DESIGN	<p>This is an open-label, single-arm study in which subjects with manifest HD who are receiving FDA-approved doses of tetrabenazine¹ (TBZ) for the treatment of chorea associated with HD or have successfully completed the SD-809-C-15 efficacy study will be invited to participate. Two groups of subjects will be enrolled into this trial:</p> <p>Switch subjects are those who are currently receiving stable doses of tetrabenazine for treatment of chorea associated with HD and convert to SD-809 ER based on an algorithm designed to achieve comparable exposure to total (α+β)-HTBZ metabolites.</p> <p>Rollover subjects are those who have successfully completed Study SD-809-C-15 and are continuing on long-term SD-809 ER after a 1-week wash out period.</p> <p>Subjects who do not already have a legally authorized representative will undergo an independent evaluation by a qualified healthcare provider to determine their capacity to provide informed consent. Informed consent/assent will be obtained before any study procedures are performed. A Research Advance Directive (See Section 6.12) will be obtained from subjects with the ability to self consent. Subjects rolling over from the SD-809-C-15 study may have capacity assessment/informed consent/assent/research advance directive obtained up to 30 days in advance of subject's First-HD Week 13 Visit/ARC-HD Baseline Visit.</p> <p>Subjects Switching from Tetrabenazine (Switch): Subjects who are currently receiving an FDA-approved dose of tetrabenazine that is providing a therapeutic benefit for chorea control may be eligible to participate in the study. Subjects in this cohort will undergo a full screening evaluation within 30 days of the Baseline assessment prior to switching to SD-809 ER (Schedule of Events A). These subjects will be converted from their TBZ regimen to an SD-809 ER regimen that is predicted to provide comparable exposure to total (α+β)-dihydrotetrabenazine (α- and β-HTBZ). Subjects will continue taking their TBZ regimen through midnight of Day 0 and then directly switch to their assigned</p>

¹ The maximum dose of tetrabenazine is 100 mg/day (with a maximum single dose of 37.5 mg), unless the subject has known impaired CYP2D6 function, in which case the maximum dose is 50 mg/day with a maximum single dose of 25 mg.

	<p>a dose level that adequately controls chorea and is well tolerated by the Week 4 visit (Switch subjects) or Week 5 telephone contact (Rollover subjects) should have unscheduled visits or telephone contacts in order to further adjust their dose upward or downward. Site interactions for dose adjustment should alternate between telephone contacts and clinic visits. During long-term treatment, further dose adjustments of SD-809 ER may be made, if necessary, but not more often than weekly. Dose adjustments should be based on all available information including the subject's and caregiver's reports of adverse events and chorea control, as well as information from rating scales and safety evaluations, when available. Long term treatment will continue until SD-809 ER becomes commercially available in the U.S.</p> <p>Post-Treatment Safety Follow Up: All subjects will discontinue study drug at the End of Treatment visit and return for their final clinic visit one week later for evaluation of safety, chorea and motor function. During this one week washout, subjects should not take prohibited concomitant medications. Subjects will also have a follow up telephone contact four weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage.</p> <p>PK Sub-Study (Switch subjects only): A sub-study will be conducted to evaluate the pharmacokinetics (PK) of tetrabenazine and SD-809 ER in Switch subjects. Approximately 12 subjects will have rich PK sampling and approximately 24 subjects will have sparse PK sampling (See PK section of synopsis). The PK of tetrabenazine and metabolites will be assessed at the Baseline visit and the PK of SD-809 and metabolites will be assessed at the Week 8 visit. If a subject requires a dose change at Week 8, the Week 8 visit assessments should be conducted except for PK sampling which should be postponed until Week 15.</p>
FORMULATION	<p>SD-809 extended release (ER) tablets will be provided in dose strengths of 6, 9 and 12 mg. Each dose strength will have a marking of SD 6, SD 9 and SD 12, corresponding to the dose strength and a distinct color: 6 mg - purple; 9 mg - blue; 12 mg - beige.</p> <ul style="list-style-type: none"> • During dose adjustment/titration, SD-809 ER will be supplied in weekly blister cards. • Once the investigator determines that a stable dose has been reached, SD-809 ER will be supplied in 30 count containers.
DOSE REGIMEN	<p><u>General guidance:</u></p> <ul style="list-style-type: none"> • All treatment regimens will be administered with meals • A daily dose of 6 mg will be given once a day in the morning and daily doses of 12 mg and higher will be administered twice daily, approximately 10 hours apart during the day. • The maximum total daily dose of SD-809 ER is 72 mg (36 mg BID), unless the subject is receiving a strong CYP2D6 inhibitor (See Appendix 11), in which case the maximum total daily dose is 42 mg <ul style="list-style-type: none"> ○ Individual doses up to and including 12 mg are given as a single tablet ○ Individual doses of 15 to 24 mg will be given as two tablets ○ Individual doses of 27 to 36 mg will be given as three tablets • Dose increases or decreases may occur no more frequently than once per week • Dose adjustments are limited to 6 mg/day (each week) (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached). Dose reductions in increments greater than 6 mg should be reviewed with the Clinical Monitor. (See Section 5.2.5) • If a strong CYP2D6 inhibitor is started (i.e., paroxetine, fluoxetine, bupropion), the Clinical Monitor should be notified as a dose reduction of more than 6 mg may be required.

DOSE REGIMEN (continued)	<u>Switch Subjects:</u>			
	<ul style="list-style-type: none"> <i>Initial dosing regimen:</i> Based on the subject’s tetrabenazine total daily dose, an initial dosing regimen of SD-809 ER will be assigned which targets a steady state AUC of total ($\alpha+\beta$)-HTBZ that is comparable to that of the subject’s tetrabenazine regimen: 			
	If a Switch Subject’s Incoming Total Daily TBZ Dose is:	Then, the Initial Total Daily SD-809 ER Dose Should Be:	Taken As:	
			Morning Dose	Evening Dose
	12.5 mg	→	6 mg	6 mg
	25 mg	→	12 mg	6 mg
	37.5 mg	→	18 mg	9 mg
	50 mg	→	24 mg	12 mg
	62.5 mg	→	30 mg	15 mg
	75 mg	→	36 mg	18 mg
87.5 mg	→	42 mg	21 mg	
100 mg	→	48 mg	24 mg	
<ul style="list-style-type: none"> The dose of SD-809 ER may be adjusted (upward or downward) in increments of 6 mg per day (each week) (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached) until a dose level that adequately controls chorea is identified, the subject experiences a protocol defined “clinically significant” adverse event (defined as related to study medication and either a) moderate or severe in intensity or b) meets the criteria for a Serious Adverse Event [SAE])¹; or the maximal allowable dose is reached. If a subject experiences a “clinically significant” AE attributable to SD-809 ER, the investigator will determine if a dose reduction or suspension is necessary. 				
<u>Rollover Subjects:</u>				
<ul style="list-style-type: none"> The starting dose will be SD-809 ER 6 mg in the AM, regardless of previous treatment in the SD-809-C-15 trial. Prior treatment assignment from Study SD-809-C-15 will remain blinded. During the titration period, the dose of SD-809 ER may be increased or decreased on a weekly basis in increments of 6 mg per day (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached) until there is adequate control of chorea; the subject experiences a protocol defined “clinically significant” adverse event (defined as related to study medication and either a) moderate or severe in intensity or b) meets the criteria for a Serious Adverse Event [SAE])¹; or the maximal allowable dose is reached. If a subject experiences a “clinically significant” AE attributable to SD-809 ER, the investigator will determine if a dose reduction or suspension is necessary. 				
<u>Long term Treatment:</u>				
For all subjects during the long-term treatment period, the dose of SD-809 ER may be adjusted (upward or downward) in increments of 6 mg per day (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached), if necessary, to optimize chorea control while minimizing adverse events. However, such changes in dose may not occur more frequently than once per week.				

¹ See Section 7 for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

	<p>childbearing potential must be using one of the following acceptable birth control methods if sexually active:</p> <ul style="list-style-type: none"> • IUD or intrauterine system in place for at least 3 months prior to screening; • Subject or partner using barrier method (e.g., condom, diaphragm, or cervical cap) with spermicide from screening through study completion; • Partner has a documented vasectomy > 6 months prior to Baseline. • Stable hormonal contraception (with approved oral, transdermal, or depot regimen) for at least 3 months prior to screening. <p>9. The subject has a reliable caregiver who interacts with the patient on a daily basis, oversees study drug administration, assures attendance at study visits and participates in evaluations, as required.</p> <ul style="list-style-type: none"> • <u>Note</u>: Subjects with a TFC score of 5-7 at Screening must have a live-in caregiver. • <u>Note</u>: Subjects with a TFC score of 5-7 at Screening <u>or</u> those who enrolled with the consent of an LAR, must have caregivers present at all study visits. • <u>Note</u>: For subjects with a TFC score of 8-13 at Screening who did not require an LAR to provide informed consent, the caregiver must attend the following visits: Screening, Baseline, Weeks 4, 8, 15, 28 and visits every 13 weeks thereafter through the End of Treatment visit. Caregivers will be encouraged to attend other visits. <p>10. Subject is able to ambulate without assistance for at least 20 yards (<u>Note</u>: The use of assistive devices (i.e., walker, cane) are permitted during ambulation).</p> <p>11. Has sufficient reading skills to comprehend the subject completed rating scales.</p>
<p>EXCLUSION CRITERIA</p>	<p>1. Subject has a serious untreated or undertreated psychiatric illness, such as depression, at Screening or Baseline.</p> <ul style="list-style-type: none"> • <u>Note</u>: Subjects receiving antidepressant therapy may be enrolled if on a stable dose for at least 8 weeks before Screening (See Appendix 12) for prohibited antidepressants). <p>2. Subject has active suicidal ideation at Screening or Baseline.</p> <p>3. Subject has history of any of the following suicidal thoughts or behavior at Screening or Baseline:</p> <ul style="list-style-type: none"> • Previous intent to act on suicidal ideation with a specific plan (positive answer to question 5 on C-SSRS), irrespective of level of ambivalence at the time of suicidal thought • Previous preparatory acts or behavior • A previous actual, interrupted or aborted suicide attempt <p>4. Subject has a score ≥ 11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) at Baseline.</p> <p>5. Subject has an unstable or serious medical or psychiatric illness at Screening or Baseline.</p> <p>6. Subject has received tetrabenazine within 7 days of Baseline (Rollover subjects).</p> <p>7. Subject has received any of the following concomitant medications within 30 days of Screening or Baseline:</p> <ul style="list-style-type: none"> • Antipsychotics (See Appendix 13) • Metoclopramide

<p>EXCLUSION CRITERIA (continued)</p>	<ul style="list-style-type: none"> • Monoamine oxidase inhibitors (MAOI) • Levodopa or dopamine agonists • Reserpine • Amantadine • Memantine (Rollover subjects <u>only</u>) <ul style="list-style-type: none"> ○ Switch subjects may receive Memantine if on a stable, approved dose for at least 30 days. <p>8. Subject has a score of ≥ 11 on the Swallowing Disturbance Questionnaire (SDQ) at Screening or Baseline.</p> <p>9. Subject has a Unified Parkinson’s Disease Rating Scale (UPDRS) dysarthria score of ≥ 3 at Screening or Baseline.</p> <p>10. Subject requires treatment with drugs known to prolong the QT interval. Note:</p> <ul style="list-style-type: none"> • Quetiapine (Seroquel) is not allowed. • Escitalopram (Lexapro or CipraleX)¹ is allowed when administered according to approved labeling. • Citalopram (Celexa)² is allowed when administered according to approved labeling. • See Appendix 16 for Celexa and Lexapro (CipraleX) dosing information • See Appendix 12 for a complete list of prohibited or restricted QT prolonging drugs. <p>11. Subject has a QTcF value >450 ms (males) or >460 ms (females), or >480 ms (with right bundle branch block) on 12-lead ECG at Screening.</p> <ul style="list-style-type: none"> • <u>Note</u>: Subjects with left bundle branch block are not eligible. <p>12. Subject has evidence of hepatic impairment at Screening, as indicated by:</p> <ul style="list-style-type: none"> • AST or ALT >2.5 times the upper limit of normal. • Alkaline phosphatase (ALP) or total bilirubin (TBil) >2 times the upper limit of normal (ULN) <ul style="list-style-type: none"> ○ <u>Note</u>: Subjects with Gilbert’s Syndrome are eligible to participate if approved by the medical monitor. ○ <u>Note</u>: Subjects with abnormalities in two or more of these analytes (AST, ALT, ALP, TBil) must be approved by the Clinical Monitor in order to be enrolled. • Prothrombin time > 4 sec prolonged. • Positive Hepatitis B surface antigen (HBsAg). <p>13. Subject has evidence of significant renal impairment at Screening, indicated by a creatinine clearance <50 mL/min, as estimated by the Cockcroft-Gault formula.</p>
--	---

¹ Escitalopram (Lexapro or CipraleX): The maximum allowed dose is 20 mg/day. The maximum dose for subjects ≥ 65 years old is 10 mg/day.

² Citalopram (Celexa) is allowed with the following restrictions (See Appendix 16):

- a) If the subject is a known CYP2C19 poor metabolizer, Celexa is not allowed.
- b) If the subject is > 60 years old or is receiving cimetidine, omeprazole, esomeprazole, fluconazole, fluoxetine or ticlopidine, the maximum allowed dose is 20 mg/day.
- c) If the subject is ≤ 60 years old and is not receiving any of the medications in (b) above, the maximum allowed dose is 40 mg.

	<p>14. Subject has known allergy to any of the components of study medication.</p> <p>15. Subject has participated in an investigational drug or device trial other than SD-809-C-15 within 30 days (or 5 drug half-lives) of Screening, whichever is longer.</p> <p>16. Subject is pregnant or breast-feeding at Screening or Baseline.</p> <p>17. Subject acknowledges present use of illicit drugs at Screening or Baseline.</p> <p>18. Subject has a history of alcohol or substance abuse in the previous 12 months, as defined in the DSM-IV, or subject is unable to refrain from substance abuse throughout the study.</p>		
<p>SAFETY PARAMETERS</p>	<table border="1"> <tr> <td data-bbox="454 871 824 1190"> <ul style="list-style-type: none"> • Adverse events (AEs) • Clinical laboratory tests • Physical examination (PE) • Vital signs • 12-lead ECGs • Epworth Sleepiness Scale (ESS) </td> <td data-bbox="824 871 1547 1190"> <ul style="list-style-type: none"> • Columbia Suicide Severity Rating Scale (C-SSRS) • Unified Huntington’s Disease Rating Scale (UHDRS) • Swallowing Disturbance Questionnaire (SDQ) • Unified Parkinson’s Disease Rating Scale (UPDRS) dysarthria item • Barnes Akathisia Rating Scale (BARS) • Hospital Anxiety and Depression Scale (HADS) • Montreal Cognitive Assessment (MoCA) </td> </tr> </table>	<ul style="list-style-type: none"> • Adverse events (AEs) • Clinical laboratory tests • Physical examination (PE) • Vital signs • 12-lead ECGs • Epworth Sleepiness Scale (ESS) 	<ul style="list-style-type: none"> • Columbia Suicide Severity Rating Scale (C-SSRS) • Unified Huntington’s Disease Rating Scale (UHDRS) • Swallowing Disturbance Questionnaire (SDQ) • Unified Parkinson’s Disease Rating Scale (UPDRS) dysarthria item • Barnes Akathisia Rating Scale (BARS) • Hospital Anxiety and Depression Scale (HADS) • Montreal Cognitive Assessment (MoCA)
<ul style="list-style-type: none"> • Adverse events (AEs) • Clinical laboratory tests • Physical examination (PE) • Vital signs • 12-lead ECGs • Epworth Sleepiness Scale (ESS) 	<ul style="list-style-type: none"> • Columbia Suicide Severity Rating Scale (C-SSRS) • Unified Huntington’s Disease Rating Scale (UHDRS) • Swallowing Disturbance Questionnaire (SDQ) • Unified Parkinson’s Disease Rating Scale (UPDRS) dysarthria item • Barnes Akathisia Rating Scale (BARS) • Hospital Anxiety and Depression Scale (HADS) • Montreal Cognitive Assessment (MoCA) 		

ENDPOINTS	<ul style="list-style-type: none">• Incidence of adverse events (AEs), serious AEs, severe AEs, drug related AEs, AEs leading to withdrawal during the following periods:<ul style="list-style-type: none">• Overall• During titration in Rollover subjects (up to 8 weeks)• During dose adjustment in Switch subjects (up to 4 weeks)• During long term treatment• Observed values and changes from baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis)• Observed values and changes from baseline in vital signs• Observed values in ECG parameters and abnormal findings• Number of subjects with on-treatment QTcF values > 450ms, > 480ms, > 500ms• Observed values and changes in UHDRS, UPDRS (dysarthria), BARS, HADS, ESS, C-SSRS, and MoCA[®]• Duration of time to achieve stable dosing of SD-809 ER
------------------	---

<p>PHARMACO-KINETICS</p>	<p>A pharmacokinetic (PK) sub-study will be conducted in subjects switching from TBZ to SD-809 ER. Blood samples will be obtained for measurement of plasma concentrations of SD-809, tetrabenazine and their respective α-HTBZ, β-HTBZ, total (α+β)-HTBZ and other metabolites, as required. Approximately one third of the PK sub-study population will have rich samples drawn and the remaining two thirds will have sparse sampling. The rich sampling cohort should be enrolled first. Subjects who are unable or unwilling to participate in the rich sampling cohort may be assigned to the sparse sampling cohort.</p> <p>Blood samples will be collected at Baseline (on tetrabenazine) and at Week 8 (on SD-809 ER) as follows:</p> <table border="1" data-bbox="467 520 1458 892"> <thead> <tr> <th>Cohort</th> <th>Visit</th> <th>Day 0 (TBZ)</th> <th>Week 8* (SD-809 ER)</th> </tr> </thead> <tbody> <tr> <td>Rich Sampling (N=12)</td> <td>Morning only</td> <td>Pre-dose, 0.5, 1, 2 and 6 hours post-dose</td> <td>Pre-dose, 1.5, 2.5, 4 and 6 hours post-dose</td> </tr> <tr> <td rowspan="2">Sparse Sampling (N=24)</td> <td>Morning</td> <td>Pre-dose and 1-2 hours post-dose</td> <td>Pre-dose and 2-4 hours post-dose</td> </tr> <tr> <td>Afternoon</td> <td>1st sample during the visit and 2nd at least 1 hr† afterward</td> <td>1st sample during the visit and 2nd at least 2 hrs† afterward</td> </tr> </tbody> </table> <p>* If a subject requires a dose change at Week 8, the Week 8 visit assessments should be conducted except for PK sampling which should be postponed until Week 15. † The second PK sample for sparse sampling (afternoon) should be taken as late as possible</p> <p>Subjects in the rich sampling cohort must have a morning visit in which the AM dose of tetrabenazine or SD-809 ER is administered in clinic. Subjects in the sparse sampling cohort may have a morning or an afternoon visit. If sparse sample subjects have a morning visit, the AM dose of tetrabenazine or SD-809 ER should be administered in clinic as with the rich sampling cohort. If the subject is assigned to the rich group at the Screening Visit but forgets to hold tetrabenazine dose the morning of the Baseline visit, the subject must be re-consented to undergo sparse sampling. If sparse sampling subjects have an afternoon visit, tetrabenazine or SD-809 ER should be taken per their usual schedule. At each time point, four (4) mL of blood will be collected into lithium heparin tubes and processed to plasma. After centrifugation, the plasma will be split into 2 aliquots and stored frozen in polypropylene plasma storage tubes at -70°C or below.</p>	Cohort	Visit	Day 0 (TBZ)	Week 8* (SD-809 ER)	Rich Sampling (N=12)	Morning only	Pre-dose, 0.5, 1, 2 and 6 hours post-dose	Pre-dose, 1.5, 2.5, 4 and 6 hours post-dose	Sparse Sampling (N=24)	Morning	Pre-dose and 1-2 hours post-dose	Pre-dose and 2-4 hours post-dose	Afternoon	1 st sample during the visit and 2 nd at least 1 hr† afterward	1 st sample during the visit and 2 nd at least 2 hrs† afterward
Cohort	Visit	Day 0 (TBZ)	Week 8* (SD-809 ER)													
Rich Sampling (N=12)	Morning only	Pre-dose, 0.5, 1, 2 and 6 hours post-dose	Pre-dose, 1.5, 2.5, 4 and 6 hours post-dose													
Sparse Sampling (N=24)	Morning	Pre-dose and 1-2 hours post-dose	Pre-dose and 2-4 hours post-dose													
	Afternoon	1 st sample during the visit and 2 nd at least 1 hr† afterward	1 st sample during the visit and 2 nd at least 2 hrs† afterward													
<p>PHARMACO-KINETICS (Continued)</p>	<p>Switch Subjects will be provided with a diary at Screening and at Week 4 to record meal and dosing times before PK sampling visits at Baseline and Week 8. Prior to clinic visits subjects will be reminded to record the start time of their last meal and the time of their last dose in their diary and to bring the diary with them to the clinic visit.</p> <p>Subjects in the rich sampling cohort and those in the sparse sampling cohort who have a morning visit should be reminded <u>not</u> to take their morning dose at home prior to their Baseline visit (tetrabenazine), and prior to their Week 8 visit (SD-809 ER) as it will be administered in clinic. Morning clinic visits should be scheduled early in the day to allow sufficient time for PK blood sampling.</p> <p><i>Subjects who withdraw early from the study should have a single blood sample collected for PK at the Early Termination Visit if the last dose was within the prior 48 hours, if possible.</i></p> <p><i>Subjects experiencing an SAE should have a single blood sample collected as soon as possible after the SAE and within 48 hours for the pharmacokinetics of α- and β-HTBZ, if</i></p>															

	<p><i>possible. The date and time of the last dose of study medication should be recorded along with the date and time of the sample collection.</i></p>
STATISTICS	<p><u>Safety:</u></p> <p>Safety data will be summarized descriptively for the overall population and based on prior treatment [SD-809 ER or placebo (Rollover subjects) or tetrabenazine (Switch subjects)]. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. The nature, frequency, and severity of adverse events will be tabulated for all subjects combined and by prior treatment. Baseline, within study, end of study, and change-from-baseline values for clinical laboratory evaluations and vital signs will be summarized as appropriate.</p> <p>Treatment-emergent adverse events and laboratory, vital sign, and ECG parameters will be summarized. In addition, change from baseline will be summarized for laboratory and vital sign parameters. Shift tables will be provided for clinical laboratory results. ECG results will be classified as normal and abnormal and summarized.</p> <p>Descriptive statistics of change-from-baseline for Rollover subjects will utilize the Baseline from Study SD-809-C-15 (C-15 Baseline) and the Baseline from the present study (C-16 Baseline), as appropriate, and will be specified in the Statistical Analysis Plan.</p> <p><u>Pharmacokinetics:</u></p> <p>A population pharmacokinetic analysis will be performed using data from all subjects switching from TBZ to SD-809 ER in this study together with data obtained from subjects in Study SD-809-C-15 to examine the pharmacokinetics of SD-809 and TBZ and to explore the potential effect of various covariates on the pharmacokinetics of SD-809 and TBZ. The population pharmacokinetic analysis will be discussed in detail in a prospective Statistical Analysis Plan.</p>

SCHEDULE OF EVENTS A – SUBJECTS SWITCHING FROM TETRABENAZINE

Study Week →	Screening			Long Term Treatment										Follow up		Unscheduled		
	Up to -4	-1	Baseline	Dose Adjustment				7	8	15	28	28 + q13 wks	End of Treatment	1 wk FU	4 wk FU			
Visit Window (days) →		± 3	0	± 1													n/a	
Visit →	Screening	T1	V1	V2	T2	T3	V3	T4	V4	V5	V6	Vx ¹⁷	End Tx/ET	FU	FFU	UV ¹⁸	UT C	
Activity Visit type →	V	TC	V	V	TC	TC	V	TC	V	V	V	V	V	V	TC	V	TC	
Evaluate/Adjust Dose				X	X	X	X									X	X ³	
Evaluate Capacity for consent	X																	
Informed Consent/Assent	X																	
Assign Subject ID	X																	
Assign Unique ID	X																	
Research Advance Directive**	X																	
Selection Criteria	X		X															
Medical History/Demographics	X																	
Vital Signs/Weight	X		X ²	X			X		X ²	X	X	X	X ²	X		X		
Physical Examination	X ⁴		X									X ⁴	X					
Complete Neurological Exam	X												X					
Height	X																	
12-lead ECG	X			X ¹⁶			X ¹⁶		X				X					
Blood sampling for PK			X ¹²						X ¹³				X ⁵			X ⁵		
Provide/Remind/Review diary Card for meal/dosing times	X ⁹	X ⁹	X ¹¹				X ¹⁰	X ¹⁰	X ¹¹									
Chemistry/Hematology/UA	X*		X						X		X	X	X					
CAG Repeat	X																	
Blinded CYP2D6 Genotype	X																	
Virology Screen (HBsAg)	X																	
Pregnancy Test/FSH ⁶	S		U								U	U	U					
HADS			X	X			X		X	X	X	X	X	X				
C-SSRS ⁷	X		X	X			X		X	X	X	X	X	X				
MoCA ⁶			X				X		X	X	X	X	X	X				
UHDRS - Motor	X		X	X			X		X	X	X	X	X	X		X		
UHDRS - Cognitive			X	X			X		X	X	X	X	X	X				
UHDRS - Behavior			X	X			X		X	X	X	X	X	X				
UHDRS - Functional Assessment			X								X		X					
UHDRS - Independence			X								X		X					
UHDRS - TFC	X		X								X	X	X					
UHDRS - Summary			X								X		X					
UPDRS - Dysarthria	X		X	X			X		X	X	X	X	X	X				
SDQ	X		X	X			X		X	X	X	X	X	X				
BARS			X	X			X		X	X	X	X	X	X				
ESS			X	X			X		X	X	X	X	X	X				
Dispense/Order Study Drug ⁸		X	X	X	X	X	X		X	X	X	X					X ³	
Drug Acct/Compliance				X			X		X	X	X	X	X					
Assess Adverse Events			X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Assess Concomitant Meds	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Administer TBZ or SD-809 ER			X ¹⁴						X ¹⁵									
Evaluate Chorea Control (subject/caregiver)	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	

	Screening			Long Term Treatment										Follow up		Unscheduled		
	Up to -4	-1	Baseline ₁	1	2	3	4	7	8	15	28	28 + q13 wks	End of Treatment	1 wk FU	4 wk FU			
Study Week →																		
Visit Window (days) →		± 3	0	± 1		± 3												n/a
Visit →	Screening	T1	V1	V2	T2	T3	V3	T4	V4	V5	V6	Vx ¹⁷	End Tx/ET	FU	FFU	UV ¹⁸	UT C	
Activity Visit type →	V	TC	V	V	TC	TC	V	TC	V	V	V	V	V	V	TC	V	TC	
Return Study Drug													X					

SCHEDULE OF EVENTS KEY SUBJECTS SWITCHING FROM TETRABENAZINE

- [V] Clinic Visit
- [TC] Telephone Contact
- [ET] Early Termination Visit
- [FU] Follow Up Visit one week after end of treatment
- [FFU] Final Follow Up Visit four weeks after end of treatment
- [S] Serum pregnancy test for women of childbearing potential only
- [U] Urine pregnancy test for women of childbearing potential only

* Screening labs to include Prothrombin Time (PT) with INR

** Subjects who have the capacity to provide informed consent only (See Section 6.12)

- 1 Baseline visit (Day 0) will occur on the day before the scheduled first dose of SD-809 ER (Day 1)
- 2 Perform orthostatic blood pressure and pulse after subject is in standing position for at least 3 minutes.
- 3 Assessments to be completed at Investigator's discretion
- 4 Brief physical examination, which includes evaluation of the cardiovascular, respiratory, and abdominal systems.
- 5 Subjects who withdraw early from the study should have a single blood sample collected for PK at the Early Termination Visit if the last dose was within the prior 48 hours, if possible. Subjects who experience an SAE should have a single blood sample collected for metabolites of SD-809 within 48 hours of SAE, if possible
- 6 Serum follicle stimulating hormone (FSH) level to be assessed in post-menopausal females only (at Screening only).
- 7 At Screening, administer the C-SSRS Baseline version. At Baseline and every visit thereafter, administer the C-SSRS Since Last Visit version.
- 8 Study medication supply will be ordered. (See Operations Manual for further details).
- 9 Provide Diary Card to record meals and tetrabenazine dosing times for upcoming PK sampling day. Subjects should be reminded approx. 7 days before next scheduled visit to complete diary card. Subjects in the "**Rich**" cohort and "**Sparse**" cohort, scheduled for a morning visit, will be reminded to hold dose of tetrabenazine on the day of their Baseline visit. Subjects in the "**Sparse**" cohort, scheduled for an afternoon visit, will be reminded to take their usual dose(s) of tetrabenazine at home per their usual schedule on the day of their Baseline visit.
- 10 Provide diary card to record the start time of the subject's last meal and the time of their last dose of SD-809 ER prior to the Week 8 visit and ask the subject to bring the diary card with them to the next clinic visit. Subjects should be reminded approx. 7 days before next scheduled visit to complete diary card. Subjects in the "**Rich**" cohort and "**Sparse**" cohort, scheduled for a morning visit, will be reminded to hold dose of SD-809 ER on the day of their Week 8 visit. Subjects in the "**Sparse**" cohort, scheduled for an afternoon visit, will be reminded to take their usual dose(s) of SD-809 ER at home per their usual schedule on the day of their Week 8 visit.
- 11 Collect and review diary card
- 12 PK blood sample for tetrabenazine and metabolites
- 13 PK blood sample for SD-809 and metabolites. If subject requires a dose change at Week 8, PK sampling should be postponed until Week 15.
- 14 Administer tetrabenazine in clinic if subject scheduled for morning visit. If subject is scheduled for afternoon visit, they will take their usual dose of tetrabenazine at home.
- 15 Administer SD-809 ER in clinic if subject scheduled for morning visit. If subject is scheduled for afternoon visit, they will take their usual dose of SD-809 ER at home.
- 16 For subjects on allowed doses of Celexa or Lexapro (Ciprallex):
 - Week 1: A 12-lead ECG is required at this visit.
 - Week 4: If the dose of study drug has been increased since the last ECG, a 12-lead ECG is required at this visit.
- 17 After Week 28, perform clinic visits every 13 weeks until the End of Treatment Visit. Obtain safety labs and urine pregnancy test every 26 weeks after Week 28, and perform UHDRS-TFC every 52 weeks after Week 28.
- 18 For subjects requiring an Unscheduled Clinic Visit for any reason, assessments denoted with X should be performed; all other assessments are as indicated at Investigator's discretion (see Section xxx).

SCHEDULE OF EVENTS B – SUBJECTS *ROLLING OVER* FROM SD-809-C-15

Study Week →	Screening		Long Term Treatment										Follow up		Unscheduled	
		Baseline‡	1	2	3	4	5	8	15	28	28 + q13 wks	End of Treatment	1 wk FU	4 wk FU		
Visit Window (days) →		+3	± 1													n/a
Visit →	Prior Data from Study C-15†	V1	T1	V2	T2	V3	T3	V4	V5	V6	Vx ⁹	End Tx/ET	FU	FFU	UV ¹⁰	UTC
Activity Visit type →		V	TC	V	TC	V	TC	V	V	V	V	V	V	TC	V	TC
Evaluate/Adjust Dose			X	X	X	X	X	X							X	X ³
Evaluate Capacity for consent		X§ [#]														
Informed Consent/Assent		X§														
Research Advance Directive††		X§														
Screening/Demographics		X														
Selection Criteria		X														
Update Medical History		X														
Vital Signs/Weight		**		X		X		X ²	X	X	X	X ²	X		X	
Physical Examination	*									X ⁴		X				
Complete Neurological Exam	*											X				
Height	*															
12-lead ECG	*			X ⁸		X ⁸		X				X				
Blood sampling for PK												X ⁷			X ⁷	
Chemistry/Hematology/UA	*							X		X	X	X				
CAG Repeat ¹	*															
Blinded CYP2D6 Genotype ¹	*															
Pregnancy Test		U								U	U	U				
HADS		**		X		X		X	X	X	X	X	X			
C-SSRS ⁵		**		X		X		X	X	X	X	X	X			
MoCA [©]		X				X		X	X	X	X	X	X			
UHDRS - Motor		**		X		X		X	X	X	X	X	X		X	
UHDRS – Cognitive		X				X		X	X	X	X	X	X			
UHDRS – Behavior		X		X		X		X	X	X	X	X	X			
UHDRS - Functional Assessment	*									X		X				
UHDRS – Independence	*									X		X				
UHDRS – TFC	*									X	X	X				
UHDRS - Summary	*									X		X				
UPDRS - Dysarthria		**		X		X		X	X	X	X	X	X			
SDQ		**		X		X		X	X	X	X	X	X			
BARS		**		X		X		X	X	X	X	X	X			
ESS		**		X		X		X	X	X	X	X	X			
Dispense/Order Study Drug ⁶		X	X	X	X	X	X	X	X	X	X	X				X ³
Drug Accountability/Compliance				X		X		X	X	X	X	X				
Assess Adverse Events	*		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Concomitant Meds	*		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluate Chorea Control (subject/caregiver)			X	X	X	X	X	X	X	X	X	X	X		X	X
Return Study Drug												X				

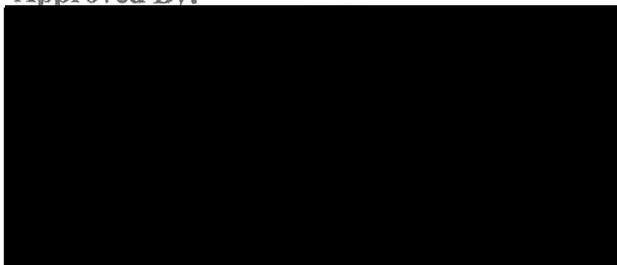
SCHEDULE OF EVENTS KEY – SUBJECTS ROLLING OVER FROM SD-809-C-15

- [V] Clinic Visit
- [TC] Telephone Contact
- [ET] Early Termination Visit
- [FU] Follow Up Visit one week after end of treatment
- [FFU] Final Follow Up Visit four weeks after end of treatment
- [U] Urine pregnancy test for women of childbearing potential only
- † After Informed Consent is obtained, data from Study SD-809-C-15 will be utilized in this study as part of screening information as detailed in the informed consent/assent.
- †† Subjects who have the capacity to provide informed consent only (See Section 6.12)
- ‡ Data from the Week 13 evaluation of Study SD-809-C-15 will provide some of the Baseline data for the present study, although such data will not become available for this study until informed consent/assent has been provided.
- § May be performed up to 30 days in advance of Baseline
- # For subjects who were determined to have the capacity to provide informed consent in Study SD-809-C-15.
- * Data (Week 12 or earlier) from Study SD-809-C-15 will be utilized in this study as part of screening information.
- ** Data (Week 13) from Study SD-809-C-15 will be utilized as part of Baseline assessment. Additional specific activities required at this visit are denoted by an “X”
- 1 Assessment transferred from Screening or Baseline evaluation in Study SD-809-C-15
- 2 Perform orthostatic blood pressure and pulse after subject is in standing position for at least 3 minutes.
- 3 Assessments to be completed at Investigator’s discretion
- 4 Brief physical examination, which includes evaluation of the cardiovascular, respiratory, and abdominal systems.
- 5 The C-SSRS Since Last Visit version is administered at all visits for Rollover subjects
- 6 Study medication supply will be ordered (See Operations Manual for further details).
- 7 Subjects who withdraw early from the study should have a single blood sample collected for PK at the Early Termination Visit if the last dose was within the prior 48 hours, if possible. Subjects who experience an SAE should have a single blood sample collected for metabolites of SD-809 within 48 hours of SAE, if possible.
- 8 For subjects on allowed doses of Celexa or Lexapro (Cipralext):
- Week 2: A 12-lead ECG is required at this visit.
 - Week 4: If the dose of study drug has been increased since the last ECG, a 12-lead ECG is required at this visit.
- 9 After Week 28, perform clinic visits every 13 weeks until the End of Treatment Visit. Obtain safety labs and urine pregnancy test every 26 weeks after Week 28, and perform UHDRS-TFC every 52 weeks after Week 28.
- 10 For subjects requiring an Unscheduled Clinic Visit for any reason, assessments denoted with X should be performed; all other assessments are as indicated at Investigator’s discretion.

PROTOCOL SIGNATURE PAGE

**AN OPEN-LABEL, LONG TERM SAFETY STUDY OF
SD-809 ER IN SUBJECTS WITH CHOREA ASSOCIATED WITH
HUNTINGTON DISEASE**

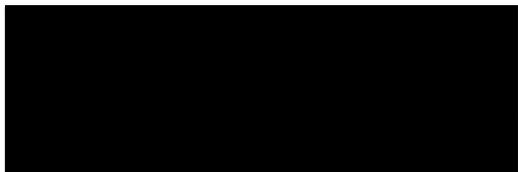
Approved By:



3/2/15

Date

Auspex Pharmaceuticals, Inc.



3/2/15

Date

Principal Investigator for the Study

TABLE OF CONTENTS

STUDY CONTACTS	2
PROTOCOL SYNOPSIS	3
SCHEDULE OF EVENTS A – SUBJECTS <i>SWITCHING</i> FROM TETRABENAZINE.....	14
SCHEDULE OF EVENTS B – SUBJECTS <i>ROLLING OVER</i> FROM SD-809-C-15	17
PROTOCOL SIGNATURE PAGE	19
TABLE OF CONTENTS.....	20
LIST OF APPENDICES.....	24
LIST OF ABBREVIATIONS.....	25
1 INTRODUCTION.....	28
1.1 Disease Background.....	28
1.2 Tetrabenazine	28
1.3 Deuterium.....	29
1.3.1 Clinical Experience with Deuterium.....	29
1.4 SD-809 (d ₆ -Tetrabenazine)	30
2 STUDY OBJECTIVES	31
3 INVESTIGATIONAL PLAN.....	31
3.1 Study Design	31
3.2 Rationale for Study Design	34
3.3 Rationale for Dose Selection.....	35
4 STUDY POPULATION.....	35
4.1 Population Characteristics.....	35
4.2 Inclusion Criteria.....	35
4.3 Exclusion Criteria.....	37
5 STUDY TREATMENT.....	39
5.1 Investigational Product.....	39
5.2 Treatment Regimen	39
5.2.1 General Guidelines.....	39
5.2.2 Dosing in Switch Subjects	40
5.2.3 Dosing in Rollover subjects	41
5.2.4 Dosing in Long Term Treatment (Weeks 3-54)	41
5.2.5 Dose Reduction or Suspension	42
5.3 Treatment Administration	42

5.4	Accountability of Study Drug	42
5.5	Study Drug Compliance	43
6	STUDY METHODS AND PROCEDURES	43
6.1	Screening Period	43
6.1.1	Screening Visit (up to Week -4) (Switch Subjects)	43
6.1.2	Prior Data from Study SD-809-C-15 (Rollover Subjects)	46
6.1.3	Baseline Visit (Day 0)	46
6.2	Dose Adjustment/Titration Period	48
6.2.1	Switch Subjects - Weeks 1 and 2	49
6.2.2	Rollover Subjects - Weeks 1 and 2	50
6.3	Long Term Treatment Period (up to 52 weeks)	51
6.3.1	Telephone Contacts (One week prior to Baseline visit [Switch only]; Week 3 \pm 3 days [All Subjects]; Week 5 \pm 3 days [Rollover only]; Week 7 \pm 3 days [Switch only])	52
6.3.2	Clinic Visits (Weeks 4, 8, 15, 28, and 41 [all \pm 3 days])	52
6.3.3	Clinic Visit (Week 54 \pm 3 days or Early Termination)	53
6.4	Post-Treatment Safety Follow Up	54
6.4.1	Clinic Visit (Week 55 \pm 3 days)	55
6.4.2	Telephone Contact (Week 58 \pm 3 days)	55
6.5	Unscheduled Visit(s)	55
6.6	Safety Evaluations	57
6.6.1	Demographics and Medical History	57
6.6.2	Physical Examination	57
6.6.3	Complete Neurological Examination	57
6.6.4	Vital Signs	57
6.6.5	Orthostatic Blood Pressure and Pulse	57
6.6.6	Laboratory Tests	58
6.6.7	12-lead Electrocardiogram (ECG)	58
6.6.8	Detecting Adverse Events	59
6.7	Rating Scales	59
6.7.1	Hospital Anxiety and Depression Scale (HADS)	59
6.7.2	Columbia Suicide Severity Rating Scale (C-SSRS)	59
6.7.3	Unified Huntington's Disease Rating Scale (UHDRS)	59
6.7.4	Montreal Cognitive Assessment (MoCA [®])	60
6.7.5	Unified Parkinson's Disease Rating Scale (UPDRS)	60

6.7.6	Barnes Akathisia Rating Scale (BARS).....	60
6.7.7	Epworth Sleepiness Scale (ESS).....	60
6.7.8	Swallowing Disturbance Questionnaire (SDQ).....	60
6.8	Pharmacokinetic Evaluations.....	61
6.9	Subject Restrictions.....	62
6.9.1	Concomitant Medications.....	62
6.9.2	Use of Alcohol or Sedating drugs.....	63
6.9.3	Other Restrictions.....	63
6.10	Caregiver Responsibilities.....	63
6.11	Capacity Assessment.....	63
6.12	Research Advance Directive.....	64
6.13	Withdrawal Criteria.....	64
6.14	Discontinued Subjects.....	64
6.15	Study Termination.....	64
7	ADVERSE EVENTS.....	64
7.1	Definitions.....	65
7.1.1	Adverse Event.....	65
7.1.2	Suspected Adverse Reaction.....	66
7.1.3	Adverse Reaction.....	66
7.1.4	Unexpected Adverse Event.....	66
7.1.5	Serious Adverse Event (SAE).....	66
7.2	Recording of Adverse Events.....	67
7.2.1	Recording of Non-Serious Adverse Events (AEs).....	67
7.2.2	Recording of Serious Adverse Events (SAEs).....	68
7.3	Evaluation of Adverse Events (Serious and Non-Serious).....	68
7.3.1	Severity.....	68
7.3.2	Relationship to Study Drug.....	69
7.3.3	Action Taken with Study Treatment.....	69
7.3.4	Treatment Required.....	69
7.3.5	Outcome.....	70
7.4	Procedures for Reporting Serious Adverse Events.....	70
7.4.1	Completion and Transmission of the SAE Report.....	70
7.4.2	Regulatory Reporting Requirements for SAEs.....	70

7.5	Procedures for Reporting Pregnancy Exposure and Birth Events.....	71
8	STATISTICAL PROCEDURES AND DATA ANALYSIS	71
8.1	Analysis Populations	71
8.2	Demographics and Baseline Data	71
8.3	Safety Analyses	71
8.4	Safety Endpoints	72
8.5	Sample Size	72
8.6	Pharmacokinetics	73
8.7	Protocol Deviations and Violations	73
8.8	Data Recording.....	73
8.9	Data Quality Assurance.....	73
8.10	Data Management	73
9	ADMINISTRATIVE ISSUES.....	74
9.1	Investigator Obligations	74
9.1.1	Independent Ethics Committee (IEC)/Institutional Review Board (IRB) Approval 74	
9.1.2	Written Informed Consent	74
9.1.3	Emergency Contact with Investigator.....	75
9.1.4	Ethical Considerations	75
9.1.5	Privacy Rule.....	75
9.2	Protocol Amendments	75
9.3	Records Retention	75
9.4	Study Monitoring.....	76
9.4.1	Steering Committee	76
9.4.2	Clinical Monitoring.....	76
9.5	Quality Assurance	76
10	INFORMATION DISCLOSURE AND INVENTIONS.....	77
10.1	Ownership	77
10.2	Confidentiality.....	77
10.3	Publication.....	77
11	REFERENCES	78
12	APPENDICES	80

LIST OF APPENDICES

Appendix 1: Site Investigator Signature Page	81
Appendix 2: Unified Huntington’s Disease Rating Scale (UHDRS)	82
Appendix 3: Hospital Anxiety and Depression Scale (HADS)	98
Appendix 4: Columbia Suicidality Severity Rating Scale (C-SSRS) – Baseline	100
Appendix 5: Columbia Suicidality Severity Rating Scale (C-SSRS) – Since Last Visit	104
Appendix 6: Unified Parkinson’s Disease Rating Scale (UPDRS): Speech.....	108
Appendix 7: Montreal Cognitive Assessment (MoCA [®]).....	109
Appendix 8: Epworth Sleepiness Scale (ESS).....	113
Appendix 9: Barnes Akathisia Rating Scale (BARS).....	115
Appendix 10: Swallowing Disturbance Questionnaire (SDQ).....	118
Appendix 11: Strong CYP2D6 Inhibitors.....	120
Appendix 12: Prohibited or restricted QT Prolonging Drugs.....	121
Appendix 13: Prohibited Antipsychotic Drugs.....	122
Appendix 14: Simulated Exposures of Total ($\alpha+\beta$)-HTBZ for Tetrabenazine and SD-809	123
Appendix 15: Simulated Exposures (AUC ₂₄) of Total ($\alpha+\beta$)-HTBZ for Initial SD-809 Regimens at Steady State in CYP2D6 Poor Metabolizers.....	124
Appendix 16: Celexa and Lexapro (Cipralext) Dosing Information	125

LIST OF ABBREVIATIONS

Abbreviation	Definition
\leq	Less than or equal to
\geq	Greater than or equal to
°C	Degrees Celsius
°F	Degrees Fahrenheit
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC	Area Under Curve
BARS	Barnes Akathisia Rating Scale
BID	Twice daily
BUN	Blood urea nitrogen
C	Carbon
CAG	Cytosine Adenine Guanine
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
C _{max}	Maximum concentration
CNS	Central nervous system
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCC	Clinical Trials Coordination Center
CYP2D6	Cytochrome P ₄₅₀ 2D6
CYP ₄₅₀	Cytochrome P ₄₅₀
D, d	Deuterium
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th Edition
ECG	Electrocardiogram
ER	Extended Release
ESS	Epworth Sleepiness Scale
EU	European Union

Abbreviation	Definition
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
g	Grams
GCP	Good Clinical Practice
H	Hydrogen
HADS	Hospital Anxiety and Depression Scale
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HD	Huntington disease
HIV	Human immunodeficiency virus
HTBZ	Dihydrotetrabenazine
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
Kg	Kilogram
LDH	Lactate dehydrogenase
MAO	Monoamine oxidase
MCV	Mean cell volume
mg	Milligram
min	Minute
mL	Milliliter
MoCA [®]	Montreal Cognitive Assessment
ms	Millisecond
NINDS	National Institute of Neurological Disorders & Stroke
O	Oxygen
PK	Pharmacokinetic
PR	PR interval - measured from the beginning of the P wave to the beginning of the QRS complex
QRS	QRS duration (complex) - a structure on the ECG that corresponds to the depolarization of the ventricles

Abbreviation	Definition
QT	QT interval - a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTcF	Fridericia-corrected QT interval
RBC	Red blood cell
SAE	Serious Adverse Event
SDQ	Swallowing Disturbance Questionnaire
SF-36	Short Form 36 Health Survey
SOP	Standard Operating Procedure
SSRI	Selective serotonin reuptake inhibitor
TBZ	tetrabenazine
TMC	Total maximal chorea score
TFC	Total functional capacity
t_{\max}	Time of maximum drug concentration
UHDRS	Unified Huntington's Disease Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
VMAT	Vesicular monoamine transporter

1 INTRODUCTION

1.1 *Disease Background*

Huntington disease (HD) is a fatal neurodegenerative autosomal dominant disorder characterized by progressive motor, cognitive, and behavioral symptoms that cause profound disability. The adult onset form of HD typically manifests between 35 and 40 years of age. Progression of the disease is slow and inexorable, with death ensuing approximately 10 to 20 years after onset of the first motor symptoms. The worldwide prevalence of HD is estimated to be 5-10 cases per 100,000 persons.

Histopathologically, HD is characterized by progressive loss of medium spiny neurons in the striatum and to a lesser extent of pyramidal neurons in the cortex. The disease is due to a mutation in the polyglutamine repeat sequence in the *huntingtin* gene located on Chromosome 4.

The most commonly recognized motor sign of HD is the involuntary movement chorea, which can affect all muscle groups. Chorea has the potential to interfere with daily functioning. In its early stages, chorea can contribute to impaired speaking, writing, and Activities of Daily Living (ADLs) such as feeding, dressing and bathing. In its later stages, chorea can cause gait instability and poor postural control, with an increased risk of injury from falling or flailing into objects.

Both preclinical studies in transgenic mice and clinical experience in patients with a genetic predisposition to HD implicate a relative excess of dopamine in the pathogenesis of these involuntary movements. These observations led to the development of tetrabenazine, which depletes presynaptic dopamine, as a treatment for chorea associated with Huntington disease.

1.2 *Tetrabenazine*

Tetrabenazine is approved in the United States (US), Canada and several European Union (EU) countries as a therapy for the treatment of chorea associated with Huntington disease (HD). Tetrabenazine is rapidly and extensively converted in the liver by carbonyl reductase to alpha-dihydro-tetrabenazine (α -HTBZ) and beta-dihydro-tetrabenazine (β -HTBZ). These metabolites are potent and selective inhibitors of vesicular monoamine transporter (VMAT)-2, resulting in reduced storage and release of presynaptic dopamine, and are responsible for mediating the *in vivo* efficacy of orally administered tetrabenazine.

Details on the previous experience with tetrabenazine in patients with Huntington disease can be found in the SD-809 ER Investigator's Brochure (IB), which includes the tetrabenazine prescribing information.

Limitations of the Current Commercial Product

The commercial form of tetrabenazine (Xenazine[®], Nitoman[®]) is an immediate release formulation. While generally effective in the treatment of chorea, tetrabenazine has limitations for use in Huntington disease patients, including:

- High peak concentrations of the active metabolites. Clinical experience in patients, and Phase 1 data in healthy volunteers, indicate that important adverse events of tetrabenazine, such as somnolence, akathisia, and anxiety are often associated with peak concentration after dosing.

- Short half-lives of the active metabolites and the attendant requirement to dose the immediate release formulation frequently. The rapid decline in plasma concentrations may lead to loss of efficacy at the end of the dosing interval. The fluctuation in plasma concentration, as indicated by high peak concentrations and low trough concentrations, necessitates more frequent dosing. Therefore, many patients must take tetrabenazine three times a day due to the short half-lives of the active metabolites, α -HTBZ and β -HTBZ. A less frequent dosing schedule is preferred as it may improve medication compliance.
- The active metabolites α - and β -HTBZ are either primarily (α) or exclusively (β) metabolized by CYP2D6. Polymorphisms in the CYP2D6 gene necessitate genotyping to prevent poor metabolizers from significantly greater exposure to the active drug moiety than extensive metabolizers.

To address the limitations of commercial tetrabenazine, Auspex has developed a deuterated analogue of tetrabenazine (referred to as SD-809) which, due to the deuteration, is eliminated more slowly than tetrabenazine (See below). It is also administered in an extended release formulation. As outlined in Section 1.4 and the Investigator's Brochure, SD-809 extended release (ER) has been shown to reduce plasma fluctuation and dosing frequency and thus, has the potential to improve overall tolerability as compared to tetrabenazine.

1.3 Deuterium

Deuterium (D) is a naturally-occurring, non-radioactive stable isotope of hydrogen (H) which, due to the presence of a neutron, has twice the mass as H. Deuterium has a natural abundance of approximately 0.0156% of all H atoms (1). The adult male body contains approximately 57% water (2), the major source of H in the body (3). A 70 kilogram (Kg) male contains approximately 39,900g of water of which 0.0156% or 6.22g is D₂O, yielding a naturally-occurring body content of 1.24g of deuterium.

Small molecule drugs have been developed in which carbon (C)-H bonds have been replaced with C-D bonds (4). The increased mass of deuterium in the C-D bond in small molecule drugs requires more energy for cleavage by cytochrome P₄₅₀ (CYP₄₅₀) enzymes as compared to the corresponding C-H bond, a phenomenon known as the Deuterium Kinetic Isotope Effect (1). Replacing H with D at a C-H bond in a molecule has the potential to attenuate its metabolism if that C-H bond is the site of rate limiting cleavage by a CYP isozyme. By attenuating metabolism in this manner, area under the curve (AUC), maximum concentration (C_{max}), and half-life may all be increased relative to the non-deuterated molecule (4).

The presence of D in the C-D bonds of small molecule drugs does not pose a unique safety risk. The C-D bond is more stable than the C-H bond and as such, D is not readily subject to exchange with H in H₂O or in other organic materials (4). The shape and surface charge of small molecule drugs is defined by the electron cloud of the component atoms. The surface charge and spatial characteristics of deuterated drugs are thought to be biologically indistinguishable from their non-deuterated forms (5, 6). As a consequence, deuterium-substituted small molecule drugs and their non-deuterated forms are not likely to be physiologically different in their binding to macromolecular structures such as receptors, transporters, enzymes, or ion channels.

1.3.1 Clinical Experience with Deuterium

A number of studies in healthy volunteers and patients have evaluated the effects of acute and

long term use of deuterated water (D₂O). Acute exposures of up to 23% D replacement in plasma were tolerated without reported adverse events (7). In several metabolic labeling studies healthy subjects consumed daily doses of up to 9.8g D in the form of D₂O for up to 4-9 weeks, treatments sufficient to maintain 1.0–2.0% D enrichment in body water. No adverse events were reported in these studies (8-12). Deuterium has also been delivered to humans in the form of D-substituted glucose. Twenty-five subjects with human immunodeficiency virus (HIV) and 10 control subjects were infused intravenously over 48 hours with up to 200 g of [6,6-d₂]-glucose, an amount which corresponds to 4.4 g of deuterium. These infusions were not associated with adverse events (13).

1.4 SD-809 (*d*₆-Tetrabenazine)

SD-809 is a deuterated analog of tetrabenazine in which the two O-linked methyl groups (CH₃) of the tetrabenazine molecule have been replaced by two trideuteromethyl groups (CD₃). The conversion of SD-809 and tetrabenazine to their active metabolites, α-HTBZ and β-HTBZ, proceeds similarly in human liver S9 fraction and in human liver microsomes. The CD₃ groups in SD-809, which are conserved in α-HTBZ and β-HTBZ, attenuate the metabolism of these active metabolites by CYP2D6 relative to the non-deuterated metabolites from tetrabenazine, leading to longer *in vitro* half-lives in human liver microsomes, human liver S9 fraction and in cells transfected with CYP2D6. These pharmacokinetic benefits have been confirmed in a clinical setting and enable less frequent dosing and reduced the plasma fluctuation of the active metabolites. Furthermore, the attenuated metabolism achieved through deuteration reduces the impact of CYP2D6 genotype on exposure as compared to tetrabenazine, with the potential to simplify dosing.

The safety and pharmacokinetics of oral SD-809 have been evaluated in five Phase 1 studies in healthy adult volunteers. Single doses of SD-809 (either as an immediate-release or as an extended-release [ER] formulation) have been administered to 130 subjects at doses ranging from 7.5 to 24 mg, either alone or in conjunction with CYP2D6 inhibition. Multiple dose regimens of the ER formulation have also been administered to 24 of those subjects for up to 5 days (at doses up to 22.5 mg twice daily [BID] for 3 days).

For all studies, plasma concentrations of parent drug were low and sporadic because of the rapid and extensive hepatic metabolism of SD-809 to the active metabolites *d*₆-α-HTBZ and *d*₆-β-HTBZ. Peak plasma concentrations of the active moieties *d*₆-α-HTBZ and *d*₆-β-HTBZ were reached within 1 to 1½ hours post-dosing following administration of an immediate release formulation. Peak plasma concentrations were significantly later (median *t*_{max} 3 to 4 hours) and lower for the ER formulation without a comparable loss of exposure. In all studies where tetrabenazine was included as a control arm, deuteration was shown to significantly prolong the half-lives of both α - and β-HTBZ, resulting in an increase in exposure (~130% increase) for both active metabolites at comparable doses. Based on the pharmacokinetics over a dose range of 7.5-22.5 mg SD-809 ER, it is estimated that a 6 mg dose of SD-809 will provide an exposure (AUC_(inf)) comparable to 12.5 mg of tetrabenazine. Inhibition of CYP2D6 metabolism by paroxetine administration led to a 3-fold increase in bioavailability of *d*₆-(α+β)-HTBZ, comparatively less than has been reported with in a similar drug interaction study with tetrabenazine.

To date, five Phase 1 studies in healthy volunteers have been conducted with SD-809, including two with an immediate release formulation (powder in capsule) (AUS-SD-809-CTP-06, SD-809-C-12) and three with extended release formulations (AUS-SD-809-CTP-07 Part 1 and Part 2 and

SD-809-C-08, SD-809-C-11). In total, 100 subjects have received single doses of SD-809 or SD-809 ER, ranging from 7.5 to 22.5 mg and 24 subjects have received repeated doses of SD-809 ER for up to 5 days at 22.5 mg BID. In these studies, no SAEs were reported and all AEs were mild to moderate in intensity. Commonly reported AEs included headache, somnolence, nausea, dizziness and vessel puncture reaction. When tetrabenazine was used as a comparator, the adverse events of SD-809 were qualitatively similar to tetrabenazine. The adverse events reported with SD-809 were also consistent with prior clinical experience with tetrabenazine.

Additional information on the study results may be found in the SD-809 ER Investigator's Brochure.

A well controlled study of SD-809 ER is presently being conducted in subjects with chorea associated with HD (Study SD-809-C-15: A Randomized, Double Blind, Placebo Controlled Study of SD-809 Extended Release for the Treatment of Chorea associated with Huntington Disease). Subjects who successfully complete Study SD-809-C-15 are candidates to participate in this open label safety study. In addition, subjects on stable, FDA-approved doses of TBZ will also be considered for this study.

2 STUDY OBJECTIVES

The objectives of this study are:

1. Evaluate the safety and tolerability of titration and maintenance therapy with SD-809 ER
2. Evaluate the safety and tolerability of switching subjects from tetrabenazine to SD-809 ER
3. Evaluate the pharmacokinetics of tetrabenazine, SD-809 and their respective α - and β -HTBZ metabolites in subjects switching from tetrabenazine to SD-809 ER

3 INVESTIGATIONAL PLAN

This is an open-label, single-arm study designed to evaluate the long term safety and tolerability of SD-809 ER dose adjustments/titrations for the treatment of chorea associated with HD over long term treatment. Approximately 116 subjects who are receiving FDA-approved doses of tetrabenazine for treatment of chorea (approx. 36) or have successfully completed the SD-809-C-15 efficacy study (approx. 80) will be enrolled. The study will be conducted at approximately 40 centers in the U.S., Canada, and Australia. The study is divided into a screening period, a dose adjustment/titration period, a long term treatment period and a post-treatment safety follow up period. Overall study participation will continue until SD-809 ER becomes commercially available in the U.S.

3.1 Study Design

This is an open-label, single-arm study in which subjects with manifest HD who are receiving FDA-approved doses of tetrabenazine¹ for treatment of chorea associated with HD or have successfully completed the SD-809-C-15 efficacy study will be invited to participate. Successful completion of Study SD-809-C-15 is defined as (1) study participation through Week 13 (2) the

¹ The maximum dose of tetrabenazine is 100 mg/day (with a maximum single dose of 37.5 mg), unless the subject has known impaired CYP2D6 function, in which case the maximum dose is 50 mg/day with a maximum single dose of 25 mg.

subject has generally been compliant with study medication and procedures, in the opinion of the investigator and (3) the subject has no ongoing adverse events that are serious (SAE)¹, severe in intensity or are expected to interfere with safety evaluations in this study. Two groups of subjects will be enrolled into this trial:

Switch subjects are those who are currently receiving stable doses of tetrabenazine for treatment of chorea associated with HD and convert to SD-809 ER based on an algorithm designed to achieve comparable exposure to total ($\alpha+\beta$)-HTBZ metabolites.

Rollover subjects are those who have successfully completed Study SD-809-C-15 and may be eligible to continue on long-term SD-809 ER after a 1-week wash out period.

Subjects who do not already have a legally authorized representative will undergo an independent evaluation by a qualified healthcare provider to determine their capacity to provide informed consent prior to consent/assent process. Informed consent/assent will be obtained before any study procedures are performed. A Research Advance Directive (See Section 6.12) will be obtained from subjects with the ability to self consent. Subjects rolling over from the SD-809-C-15 study may have capacity assessment (if necessary)/informed consent/assent and Research Advance Directive (if applicable) (See Section 6.12) obtained up to 30 days in advance of subject's First-HD Week 13 Visit/ARC-HD Baseline Visit. Subjects who meet the selection criteria will be eligible to participate.

Subjects Switching from Tetrabenazine (Switch): Subjects who are currently receiving an FDA approved dose of tetrabenazine (TBZ) that is providing a therapeutic benefit for chorea control associated with HD will be eligible to participate in the study. Subjects in this cohort will undergo a full screening evaluation within 30 days of the Baseline assessment prior to switching to SD-809 ER. See Schedule of Events A. These subjects will be converted from their TBZ regimen to an SD-809 ER regimen that is predicted to provide comparable exposure to total ($\alpha+\beta$)-dihydro-tetrabenazine (α - and β -HTBZ). Subjects will continue taking their TBZ regimen through midnight of Day 0 and then directly switch to their assigned SD-809 ER regimen the next morning. The dose of SD-809 ER may be adjusted weekly (upward or downward) in increments of 6 mg per day (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached) to identify a dose level that adequately controls chorea, the subject experiences a protocol defined "clinically significant" adverse event (defined as related to study medication and either a) moderate or severe in intensity or b) meets the criteria for a Serious Adverse Event [SAE])¹; or the maximal allowable dose is reached. If a subject experiences a "clinically significant" AE attributable to SD-809 ER, the investigator will determine if a dose reduction or suspension is necessary. The investigator, in consultation with the subject and caregiver, will determine when an adequate level of chorea control has been achieved. Subjects will have a clinic visit at Week 1 and a telephone contact at Week 2, in order to evaluate safety and establish an optimal dose. Although subjects will enter the Long term treatment period after Week 2, dose adjustment (upward or downward) may continue through Week 4 to optimize dose level. Additional dose adjustments may be made after Week 4 if clinically indicated.

Subjects Enrolled from the SD-809-C-15 Study (Rollover): Subjects who have successfully completed Study SD-809-C-15 may be eligible to rollover directly into this study after they complete a one week washout and the Week 13 evaluation of Study SD-809-C-15. To reduce subject burden, after obtaining capacity assessment (if applicable)/informed consent/assent and

¹ See Section 7 for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

Research Advance Directive (if applicable), some data collected in the SD-809-C-15 study will be utilized in the SD-809-C-16 study and will provide some of the baseline data for SD-809-C-16 (See Schedule of Events B). In addition to assessments completed for the SD-809-C-15 Week 13 visit, evaluations required as part of the SD-809-C-16 study will be completed on the same day as the Week 13 visit. All subjects are expected to rollover to SD-809-C-16 at the Week 13 visit of SD-809-C-15.

As Rollover subjects will have discontinued study drug (SD-809 ER or placebo) for 1 week at completion of the SD-809-C-15 study, they will undergo titration on SD-809 ER. During titration, the investigator, in consultation with the subject and caregiver, will determine when an adequate level of chorea control has been achieved. The dose of SD-809 ER may be adjusted (upward or downward), in increments of 6 mg per day (each week) (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached), until there is adequate control of chorea; the subject experiences a protocol defined “clinically significant” adverse event (defined as related to study medication and either a) moderate or severe in intensity or b) meets the criteria for a Serious Adverse Event [SAE])¹, or the maximal allowable dose is reached. If a subject experiences a “clinically significant” AE attributable to SD-809 ER, the investigator will determine if a dose reduction or suspension is necessary. Subjects will have a telephone contact at Week 1 and a clinic visit at Week 2, in order to evaluate safety and establish a dose of study drug that adequately controls chorea and is well-tolerated. Although subjects will enter the Long term treatment period after Week 2, titration may continue through Week 8 to optimize dose level. Additional dose adjustments may be made after Week 8 if clinically indicated.

Long-Term Treatment Period: During long term treatment, all subjects will be contacted by telephone at Week 3 (the first week of Long-term treatment period) and will return to the clinic on Weeks 4, 8, 15, 28 and every 13 weeks thereafter for evaluation of safety and chorea control. Switch subjects will have an additional telephone contact at Week 7. Rollover subjects will have an additional telephone contact at Week 5. Subjects who have not achieved a stable dose by the Week 4 visit (Switch subjects) or Week 5 telephone contact (Rollover subjects) may have unscheduled visits or telephone contacts in order to further adjust their dose upward or downward. Site interactions for dose adjustment should alternate between telephone contacts and clinic visits. During long-term treatment, further dose adjustments of SD-809 ER may be made, if necessary, but not more often than weekly. Dose adjustments should be based on all available information including the subject’s and caregiver’s reports of adverse events and chorea control, information from rating scales and all safety evaluations. Long term treatment will continue until SD-809 ER becomes commercially available in the U.S.

Post-Treatment Safety Follow Up: All subjects will discontinue study drug at the End of Treatment visit and return for their final clinic visit one week later for evaluation of safety, cognition, behavior, chorea and motor function. During this one week washout, subjects should not take prohibited concomitant medications. After the one week washout is complete, concomitant medication use is per the discretion of the investigator. Subjects will also have a follow up telephone contact four weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage.

PK Sub-Study: A sub-study will be conducted to evaluate the pharmacokinetics (PK) of tetrabenazine and SD-809 ER in Switch subjects. Approximately 12 subjects will have rich PK sampling and approximately 24 subjects will have sparse PK sampling (See Section 6.8). The

¹ See Section 7 for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

PK of tetrabenazine and metabolites will be assessed at the Baseline visit and the PK of SD-809 ER and metabolites will be assessed at the Week 8 visit. If a subject requires a dose change at Week 8, the Week 8 visit assessments should be conducted except for PK sampling which should be postponed until Week 15.

3.2 *Rationale for Study Design*

The study is designed to evaluate the long term safety and tolerability of SD-809 ER in subjects with chorea associated with HD. Two cohorts of subjects may enter the study: 1) Rollover subjects, who successfully complete the well-controlled efficacy study (SD-809-C-15) and 2) Switch subjects, who are receiving FDA-approved doses of tetrabenazine for treatment of chorea.

Given the two groups of subjects entering this trial have different background therapy at entry; identification of their optimal dose will be approached differently. Rollover subjects from Study SD-809-C-15 will have discontinued study medication (SD-809 ER or placebo) for at least one week and consequently they will begin dosing at 6 mg/day and titrate to their optimal dose level for up to 8 weeks. In contrast, Switch subjects will be on a stable dose of TBZ at entry and will make a direct conversion to SD-809 ER overnight based on their incoming TBZ regimen. As such, Switch subjects should reach their target dose more rapidly and they are allowed up to 4 weeks to adjust their SD-809 ER regimen after conversion. Although the time to reach an optimal dose may differ between these cohorts, both groups are expected to reach a pharmacologically active dose by two weeks: Rollover subjects would be at 12 mg/day, unless they experienced adverse events or adequate chorea control; and Switch subjects would have converted to a dose level that provides comparable exposure to their incoming tetrabenazine dose, with one intervening visit to evaluate/adjust dose level. Accordingly, the long term period of the study will be deemed to have started after two weeks of treatment even though dose adjustment may continue after this point.

For both Rollover and Switch subjects, the SD-809 ER dose level should be adjusted in order to identify a dose that reduces chorea and is well-tolerated. In addition to the assessments of chorea control and tolerability by the subject, caregiver and study staff, safety evaluations that target adverse events observed in the drug class (e.g., akathisia), will be employed and considered in the dose adjustment decision. In this manner, the daily dose of study drug for treating chorea is determined individually for each subject. **Once adequate control of chorea has been achieved, the dose of study drug should not be increased further.** In general, subjects will continue the dose established during titration into the long term treatment period, but dose adjustments (upward or downward) are permitted so long as they do not occur more often than once per week.

To convert Switch subjects from stable doses of tetrabenazine to an effective dose of SD-809 ER, extensive Phase 1 work has been conducted to characterize the pharmacokinetics of both drugs and their active metabolites [total ($\alpha+\beta$)-HTBZ]. These data allowed construction of a pharmacokinetic model that permitted calculation of the plasma exposure associated with various tetrabenazine and SD-809 ER regimens. Based on a subject's incoming tetrabenazine regimen, an initial SD-809 ER regimen will be identified that provides comparable exposure (AUC) to total ($\alpha+\beta$)-HTBZ with reduced peak concentrations. Following conversion, subjects will have clinic visits at Weeks 1 and 4 and telephone contacts at Weeks 2 and 3 to optimize dose level.

Rollover subjects will begin treatment at the lowest SD-809 ER dose of 6 mg/day and undergo

titration/evaluation on a weekly basis for chorea control, adverse events, and possible dose adjustment. Subjects will have clinic visits at Weeks 2 and 4 and telephone contacts at Weeks 1, 3, and 5 to optimize dose level.

The present investigation is an open label safety study of long term treatment with SD-809 ER at a pharmacologically active dose and will enroll subjects with chorea associated with HD who were either previously exposed to SD-809 ER or placebo (from Study SD-809-C-15, First-HD); or who are switching directly from TBZ to SD-809 ER. It is, therefore, adequate to characterize the safety and tolerability of titration and maintenance therapy with SD-809 ER in the target population.

The U.S. prescribing information for tetrabenazine indicates that CYP2D6 genotyping should be performed at dose levels higher than 50 mg, although genotyping is often not performed in clinical practice as the drug is titrated. In the present study, CYP2D6 genotyping will be performed in a blinded manner to allow evaluation of the effect of phenotype on safety parameters at the conclusion of the study.

3.3 Rationale for Dose Selection

As with tetrabenazine, SD-809 ER treatment will be individualized, and, therefore fixed doses will not be evaluated in the study. The starting dose of 6 mg of SD-809 ER provides an AUC of total ($\alpha+\beta$)-HTBZ that is comparable to the 12.5 mg starting dose of tetrabenazine, but with a lower peak concentration and higher trough concentration. The dose level of SD-809 ER treatment will be evaluated on a weekly basis during the titration/dose adjustment period, based on assessments of chorea control and adverse events, in order to determine if dose adjustment is needed. This approach is consistent with the tetrabenazine prescribing information.

Dose adjustments should occur in increments of 6 mg/day (each week) (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached). Dose reductions in increments greater than 6 mg should be reviewed with the Clinical Monitor (See Section 5.2.5).

The maximum total daily dose of SD-809 ER is 72 mg per day, unless the subject is receiving a strong CYP2D6 inhibitor (e.g., paroxetine, See Appendix 11), in which case the maximum total daily dose is 42 mg.

4 STUDY POPULATION

4.1 Population Characteristics

Male and female adult subjects with HD who are receiving approved doses of tetrabenazine¹ for treatment of chorea or have successfully completed the SD-809-C-15 efficacy study and meet eligibility criteria will be enrolled.

4.2 Inclusion Criteria

1. Subject is at least 18 years of age or the age of majority (whichever is older) at Screening.

¹ The maximum dose of tetrabenazine is 100 mg/day (with a maximum single dose of 37.5 mg), unless the subject has known impaired CYP2D6 function, in which case the maximum dose is 50 mg/day with a maximum single dose of 25 mg.

2. Subject has been diagnosed with manifest HD, as indicated by characteristic motor exam features, and has a documented expanded CAG repeat (≥ 37) at or before Screening¹.
3. Subject meets either of the following:
 - Has successfully completed² participation in Study SD-809-C-15 OR
 - Has been receiving an FDA approved dose of tetrabenazine³ that has been stable for ≥ 8 weeks before Screening and is providing a therapeutic benefit for control of chorea
4. Subject has a Total Functional Capacity (TFC) score ≥ 5 at Screening.
5. Subject is able to swallow study medication whole.
6. Subject has provided written, informed consent or, if subject lacks the capacity to provide informed consent (as determined by an independent assessment by a qualified healthcare provider not directly involved in other study activities), a legally authorized representative (LAR) has provided written informed consent and the subject has provided assent.
7. Subject has provided a Research Advance Directive if subject has the capacity to provide informed consent (See Section 6.12).
8. Female subjects of childbearing potential⁴ agree to use an acceptable method of contraception from screening through study completion. Female subjects of childbearing potential must be using one of the following acceptable birth control methods if sexually active:
 - IUD or intrauterine system in place for at least 3 months prior to screening;
 - Subject or partner using barrier method (e.g., condom, diaphragm, or cervical cap) with spermicide from screening through study completion;
 - Partner has a documented vasectomy > 6 months prior to Baseline.

¹ A CAG repeat number obtained prior to the Screening Visit may be used to document subject eligibility if either of the following conditions are met:

- At Screening, there is documentation available in the subject's records that shows the subject has an expanded CAG repeat (≥ 37) from a prior laboratory assessment.
- At Screening, there is documentation available of a subject's prior laboratory assessment of an allele length that states a subject has a genotype consistent with a diagnosis of HD (i.e., laboratory analysis confirming the CAG repeat number was at least 40).

Note: If neither condition above is met, results from the CAG repeat sample collected at the Screening Visit must be used to determine study eligibility. A CAG Repeat Number of ≥ 37 must be documented prior to enrolling a subject into the study.

Note: Regardless of whether a prior CAG result is available, all Switch subjects will undergo CAG repeat testing at the Screening Visit, and any enrolled subject whose CAG repeat is found not to be ≥ 37 will be withdrawn from the study.

² Successful completion of Study SD-809-C-15 is defined as (1) study participation through Week 13 (2) the subject has generally been compliant with study medication and procedures, in the opinion of the investigator and (3) the subject has no ongoing adverse events that are serious (SAE) or severe in intensity or are expected to interfere with safety evaluations in this study.

³ The maximum dose of tetrabenazine is 100 mg/day (with a maximum single dose of 37.5 mg), unless the subject has known impaired CYP2D6 function, in which case the maximum dose is 50 mg/day with a maximum single dose of 25 mg.

⁴ Non-childbearing potential for females is defined as postmenopausal (amenorrheic for at least 1 year and serum follicle stimulating hormone (FSH) level consistent with postmenopausal status), or a documented hysterectomy; bilateral oophorectomy; or bilateral tubal ligation ≥ 6 months prior to study initiation.

- Stable hormonal contraception (with approved oral, transdermal, or depot regimen) for at least 3 months prior to screening.
9. The subject has a reliable caregiver who interacts with the patient on a daily basis, oversees study drug administration, assures attendance at study visits and participates in evaluations, as required.
 - Note: Subjects with a TFC score of 5-7 at Screening must have a live-in caregiver
 - Note: Subjects with a TFC score of 5-7 at Screening or those who enrolled with the consent of an LAR, must have caregivers present at all study visits.
 - Note: For subjects with a TFC score of 8-13 at Screening who did not require an LAR to provide informed consent, the caregiver must attend the following visits: Screening, Baseline, Weeks 4, 8, 15, 28 and visits every 13 weeks thereafter through the End of Treatment visit. Caregivers will be encouraged to attend other visits.
 10. Subject is able to ambulate without assistance for at least 20 yards (Note: The use of assistive devices (i.e., walker, cane) are permitted during ambulation).
 11. Has sufficient reading skills to comprehend the subject completed rating scales.

4.3 *Exclusion Criteria*

Subjects meeting any of the following criteria will be excluded:

1. Subject has a serious untreated or undertreated psychiatric illness, such as depression, at Screening or Baseline.
 - Note: Subjects receiving antidepressant therapy may be enrolled if on a stable dose for at least 8 weeks before Screening (See Appendix 12) for prohibited antidepressants).
2. Subject has active suicidal ideation at Screening or Baseline.
3. Subject has history of any of the following suicidal thoughts or behavior at Screening or Baseline:
 - Previous intent to act on suicidal ideation with a specific plan (positive answer to question 5 on C-SSRS), irrespective of level of ambivalence at the time of suicidal thought
 - Previous preparatory acts or behavior
 - A previous actual, interrupted or aborted suicide attempt
4. Subject has a score ≥ 11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) at Baseline.
5. Subject has an unstable or serious medical or psychiatric illness at Screening or Baseline.
6. Subject has received tetrabenazine within 7 days of Baseline (Rollover subjects).
7. Subject has received any of the following concomitant medications within 30 days of Screening or Baseline:
 - Antipsychotics (See [Appendix 13](#))
 - Metoclopramide
 - Monoamine oxidase inhibitors (MAOI)
 - Levodopa or dopamine agonists

- Reserpine
 - Amantadine
 - Memantine (Rollover subjects only)
 - Switch subjects may receive Memantine if on a stable, approved dose for at least 30 days.
8. Subject has a score of ≥ 11 on the Swallowing Disturbance Questionnaire (SDQ) at Screening or Baseline.
9. Subject has a Unified Parkinson's Disease Rating Scale (UPDRS) dysarthria score of ≥ 3 at Screening or Baseline.
10. Subject requires treatment with drugs known to prolong the QT interval. Note:
- Quetiapine (Seroquel) is not allowed.
 - Escitalopram (Lexapro or Cipralex)¹ is allowed when administered according to approved labeling.
 - Citalopram (Celexa)² is allowed when administered according to approved labeling.
 - See [Appendix 16](#) for Celexa and Lexapro (Cipralex) dosing information
 - See Appendix 12 for a complete list of prohibited or restricted QT prolonging drugs.
11. Subject has a QTcF value >450 ms (males) or >460 ms (females), or >480 ms (with right bundle branch block) on 12-lead ECG at Screening.
- Note: Subjects with left bundle branch block are not eligible.
12. Subject has evidence of hepatic impairment at Screening, as indicated by:
- AST or ALT >2.5 times the upper limit of normal.
 - Alkaline phosphatase (ALP) or total bilirubin (TBil) >2 times the upper limit of normal (ULN)
 - Note: Subjects with Gilbert's Syndrome are eligible to participate if approved by the Clinical Monitor.
 - Note: Subjects with abnormalities in two or more of these analytes (AST, ALT, ALP, TBil) must be approved by the Clinical Monitor in order to be enrolled.
 - Prothrombin time > 4 sec prolonged.
 - Positive Hepatitis B surface antigen (HBsAg).
13. Subject has evidence of significant renal impairment at Screening, indicated by a creatinine clearance <50 mL/min, as estimated by the Cockcroft-Gault formula.
14. Subject has known allergy to any of the components of study medication.
15. Subject has participated in an investigational drug or device trial other than SD-809-C-15 within 30 days (or 5 drug half-lives) of Screening, whichever is longer.

¹ Escitalopram (Lexapro or Cipralex): The maximum allowed dose is 20 mg/day. The maximum dose for subjects ≥ 65 years old is 10 mg/day.

² Citalopram (Celexa) is allowed with the following restrictions (See Appendix 16):

- d) If the subject is a known CYP2C19 poor metabolizer, Celexa is not allowed.
- e) If the subject is > 60 years old or is receiving cimetidine, omeprazole, esomeprazole, fluconazole, fluoxetine or ticlopidine, the maximum allowed dose is 20 mg/day.
- f) If the subject is ≤ 60 years old and is not receiving any of the medications in (b) above, the maximum allowed dose is 40 mg.

16. Subject is pregnant or breast-feeding at Screening or Baseline.
17. Subject acknowledges present use of illicit drugs at Screening or Baseline.
18. Subject has a history of alcohol or substance abuse in the previous 12 months, as defined in the DSM-IV (See Operations Manual), or subject is unable to refrain from substance abuse throughout the study.

5 STUDY TREATMENT

The study medication to be used in this trial is an extended release (ER) formulation of SD-809. Three dose strengths of SD-809 ER will be available for use: 6, 9, and 12 mg tablets. Each dose strength will have a black marking of SD 6, SD 9 or SD 12, corresponding to the dose strength and a distinct tablet color: 6 mg - purple; 9 mg - blue; 12 mg - beige.

5.1 *Investigational Product*

The investigational product is a matrix formulation and is designed as a gastro-erosional, extended release tablet to be administered with food. Study drug is coated with a colored polymer coating to aid in swallowing. The colored polymer coating is applied to the tablets according to dose strength; 6 mg - purple; 9 mg - blue; 12 mg - beige. Each dose strength will have a black marking of SD 6, SD 9 or SD 12, corresponding to the dose strength. SD-809 ER tablets have been manufactured according to current Good Manufacturing Practices regulations. During titration/dose adjustment, SD-809 ER tablets will be supplied in weekly blister packs as 6, 9, and/or 12 mg tablets and will be labeled according to applicable regulatory guidelines. Each blister pack will contain a sufficient supply of drug until the next specified visit, plus overage to account for potential delays in study visits or evaluations or receipt of their supplies. **Once the investigator determines that a stable dose has been reached, SD-809 ER will be supplied in 30 count containers and labeled according to applicable regulatory guidelines.**

Complete details regarding SD-809 ER supply, dispensing and ordering will be provided in the study Operations Manual.

SD-809 ER tablets must be stored in a secure area with access limited to authorized staff, protected from light at controlled room temperature, 15°C to 25°C (59°F to 77°F).

5.2 *Treatment Regimen*

5.2.1 *General Guidelines*

The following general guidance applies to treatment regimens for all subjects in the study:

- All treatment regimens will be administered with meals
- A daily dose of 6 mg will be given once a day in the morning and daily doses of 12 mg and higher will be administered twice daily, approximately 10 hours apart during the day.
- The maximum total daily dose of SD-809 ER is 72 mg (36 mg BID), unless the subject is receiving a strong CYP2D6 inhibitor (See Appendix 11), in which case the maximum total daily dose is 42 mg
 - Individual doses up to and including 12 mg are given as a single tablet
 - Individual doses of 15 to 24 mg will be given as two tablets
 - Individual doses of 27 to 36 mg will be given as three tablets

- Dose adjustments are limited to 6 mg/day (each week) (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached). Dose reductions in increments greater than 6 mg should be reviewed with the Clinical Monitor. (See Section 5.2.5)
- If a strong CYP2D6 inhibitor is started (i.e., paroxetine, fluoxetine, bupropion), the Clinical Monitor should be notified as a dose reduction of more than 6 mg may be required.

5.2.2 Dosing in Switch Subjects

For Switch subjects, the initial SD-809 ER dosing regimen will be based on the subject's incoming total daily dose of tetrabenazine. As outlined in Table 1 and Appendix 14, an initial dosing regimen of SD-809 ER will be assigned which targets a steady state AUC of total ($\alpha+\beta$)-HTBZ that is comparable to that of the subject's tetrabenazine regimen (Table 1).

After initial dose conversion, the investigator may adjust the dose of SD-809 ER upward or downward over the following 4 weeks, if necessary, to a level in which adequate chorea control has been achieved and the subject is tolerating the treatment regimen. Changes in dose should not be made more often than once per week unless the subject is experiencing an intolerable adverse event.

Once adequate control of chorea has been achieved, the dose of study drug should not be increased further.

Pharmacokinetic modeling and simulation of Phase 1 data were performed to estimate the overall systemic exposure (AUC) for various tetrabenazine and SD-809 ER regimens. Appendix 14 depicts the values for AUC₀₋₂₄ for extensive and intermediate metabolizers of CYP2D6.

Based on the data in Appendix 14, an initial SD-809 ER regimen has been identified which approximates the AUC₀₋₂₄ for total ($\alpha+\beta$)-HTBZ of the corresponding tetrabenazine total daily dose in CYP2D6 extensive and intermediate metabolizers (Table 1). Although the median AUCs for SD-809 ER are slightly lower than those for the corresponding tetrabenazine regimen, there is considerable overlap in the distributions of this parameter. Subjects with diminished CYP2D6 function (e.g., poor metabolizers or receiving potent CYP2D6 inhibitors) who undergo dose conversion according to Table 1 may have an initial AUC on SD-809 ER that is up to 30-40% below that of their tetrabenazine regimen (See Appendix 15). As with intermediate and extensive metabolizers, there is considerable overlap in the distribution of AUCs between SD-809 and tetrabenazine in poor metabolizers. Furthermore, subjects with inadequate control of chorea may undergo dose adjustment for the four weeks following initial dose conversion. Additional dose adjustments may be made after Week 4 if clinically indicated.

Table 1: Initial SD-809 Dose Regimen based on Incoming Tetrabenazine Regimen

If a Switch Subject's Incoming Total Daily TBZ Dose is:	Then, the Initial Total Daily SD-809 ER Dose Should Be:	Taken As:	
		Morning Dose	Evening Dose
12.5 mg	→ 6 mg	6 mg	–
25 mg	→ 12 mg	6 mg	6 mg
37.5 mg	→ 18 mg	9 mg	9 mg
50 mg	→ 24 mg	12 mg	12 mg
62.5 mg	→ 30 mg	15 mg	15 mg
75 mg	→ 36 mg	18 mg	18 mg
87.5 mg	→ 42 mg	21 mg	21 mg
100 mg	→ 48 mg	24 mg	24 mg

5.2.3 Dosing in Rollover subjects

The starting dose of SD-809 ER is 6 mg in the morning, regardless of previous treatment in the SD-809-C-15 trial. Treatment assignment (SD-809 ER or placebo) from SD-809-C-15 will remain blinded. Study drug will be titrated over the initial 8 weeks of therapy, if necessary, to identify a dose that provides adequate chorea control and is well tolerated. Changes in dose should not be made more often than once per week unless the subject is experiencing an intolerable adverse event. Additional dose adjustments may be made after week 8 if clinically indicated.

During the titration period, the dose of SD-809 ER may be increased on a weekly basis in increments of 6 mg per day (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached) until there is adequate control of chorea; the subject experiences a protocol defined “clinically significant” adverse event (defined as related to study medication and either a) moderate or severe in intensity or b) meets the criteria for a Serious Adverse Event [SAE])¹; or the maximal allowable dose is reached. If a subject experiences a “clinically significant” AE attributable to SD-809, the investigator will determine if a dose reduction or suspension is necessary.

Once adequate control of chorea has been achieved, the dose of study drug should not be increased further.

5.2.4 Dosing in Long Term Treatment

Initially during the long-term treatment period, a well-tolerated dose of SD-809 that provides adequate chorea control may not yet be established. Dose adjustments may continue during long term treatment as specified in Sections 5.2.2 and 5.2.3. Once a stable dose is achieved, SD-809 ER should be dosed at the same level throughout the remaining long term period. If necessary, however, the dose may be adjusted further during long term treatment (upward or downward) to optimize chorea control or minimize adverse events. In general, dose changes are limited to 6 mg per day (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached; See Section 5.2.5). However, such changes in dose should not occur more frequently than once per week.

Once subjects are on a stable dose of SD-809 ER, drug will be provided to study subjects in 30-count containers until the next specified visit. Each order will contain a sufficient supply of drug

¹ See Section 7 for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

until the next specified visit, plus overage to account for potential delays in study visits or evaluations or receipt of their supplies.

5.2.5 Dose Reduction or Suspension

If a subject experiences a “clinically significant” adverse event (defined below)¹ that is attributed to SD-809 ER, the investigator will use his or her judgment to determine if a dose reduction or suspension is necessary. Dose adjustments should be made based on all available information including the subject’s and caregiver’s reports of adverse events and chorea control, the clinical assessment of safety and efficacy by the investigator and information from rating scales.

Dose reductions should generally occur in increments of 6 mg/day, except in the case of addition of a strong CYP2D6 inhibitor (i.e., paroxetine, fluoxetine, bupropion) or if the most recent dose increase was 12 mg/day, in which a greater dose reduction may be required. Dose reductions in this context should be reviewed with the Clinical Monitor. A dose reduction of 6 mg/day can be made by requesting that the next lowest dose level be shipped directly to the subject. Dose reductions greater than 6 mg/day should be reviewed with the Clinical Monitor. If a subject requires a dose reduction based on a telephone contact during the maintenance period, an unscheduled clinic visit should be conducted in a timely manner thereafter.

Suspension of study medication for up to one week, if warranted, is allowed.

Suspensions of study medication for adverse events must be reviewed with the Clinical Monitor before therapy is restarted. If study medication is restarted after a suspension for an adverse event, a dose reduction of 6 mg or more is permitted.

Suspensions for more than 7 days must be reviewed by the Clinical Monitor. If the subject restarts study medication within 7 days of suspension, the full dose of SD-809 ER may be resumed without titration. If subject restarts study medication greater than 7 days following a suspension, re-titration will be required.

The reason for a dose reduction or suspension must be clearly documented.

5.3 Treatment Administration

Each tablet should be swallowed whole with water and not broken, crushed or chewed. Tablets should not be taken on an empty stomach.

Subjects should be instructed to take the investigational product with meals: tablets will be administered twice daily with meals in the morning and evening, as indicated on drug packaging. It is recommended that BID doses be taken approximately 10 hours apart during the day. A minimum of 6 hours should elapse between doses. If a subject misses a dose and it is within 6 hours of their next dose, the missed dose should be skipped.

5.4 Accountability of Study Drug

The study drug must be used in accordance with the protocol and only under the direction of the Investigator. All materials supplied are for use only in this clinical study and should not be used for any other purpose.

The Investigator is responsible for study drug accountability, reconciliation, and record

¹ See Section 7 for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

maintenance at the investigational site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received, dispensed, and disposition of unused study drug.

A Drug Dispensing/Accountability Log must be kept current and will contain the following information:

- The identification of the subject to whom the drug was dispensed;
- The date(s) and quantity of the drug dispensed to the subject.

The inventory must be available for inspection by the Sponsor and/or study monitor during the study. Drug supplies, including partially used or empty containers, will be fully accounted for by the study monitor at each visit. When requested in writing by the Sponsor or if a site does not have available storage space to hold drug, returned and unused drug supplies will be destroyed on site according to the site's standard operating procedure or returned to the Sponsor (or designee) after study drug accountability has been completed by and with approval of the study monitor. Records shall be maintained by the Investigator of any such alternate disposition of the study drug. These records must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of the study drug. Such records must be submitted to the Sponsor.

5.5 Study Drug Compliance

The investigator or designated study staff is responsible for monitoring the subject's compliance with study medication during the trial. Compliance will be assessed by tablet count, i.e., evaluation of returned study medication blister cards/containers (e.g., amount used/amount expected to be used in interval between visits) and must be reviewed at every visit while the subject is still in clinic to determine if the subject is taking study medication as directed.

Compliance will be evaluated by calculating the number of tablets used (tablets dispensed minus tablets returned) divided by the expected number of tablets to be used. A subject will be deemed compliant if the subject has taken 80-100% of the expected tablets of study drug.

6 STUDY METHODS AND PROCEDURES

6.1 Screening Period

6.1.1 Screening Visit (up to Week -4) (Switch Subjects)

See the Schedule of Events A for a detailed summary of activities.

Prior to conduct of any study-specific screening procedures, the Investigator, or designee, will explain to the subject and caregiver the study procedures, including the risks involved and the fact that their participation is voluntary. If the subject lacks the capacity to provide informed consent (as determined by an independent assessment by a qualified healthcare provider not directly involved in other study activities), a legally authorized representative must provide written informed consent and the subject must provide assent. Each subject and caregiver will acknowledge receipt of this information by signing and dating a current, IRB/IEC-approved written informed consent, or subject assent if an LAR is utilized, for their involvement in the study in the presence of the Investigator, or designee, who will also sign and date the informed consent or assent. A Research Advance Directive (See Section 6.12) will be obtained from

subjects with the ability to self consent. Subjects rolling over from the SD-809-C-15 study may have capacity assessment/informed consent/assent/research advance directive obtained up to 30 days in advance of subject's First-HD Week 13 Visit/ARC-HD Baseline Visit.

Each potentially eligible subject who has signed an informed consent or assent and is screened will be assigned a Subject Identification (ID) Number in consecutive order by the site from the site-specific Subject Identification list provided to the site by the Clinical Trials Coordination Center (CTCC); this four-digit number will identify subjects on all study forms and lab specimens. Should the subject proceed to enrollment, the Subject ID Number will continue to be used for the subject through the duration of the study. For subjects who have signed the informed consent form and subsequently do not meet eligibility criteria or withdraw consent, the source record should contain at least minimum information as documentation of screen failure (i.e., demographics, eligibility criteria reviewed, procedures performed, etc.).

In addition, subjects will be assigned a 9-digit Unique ID Number at the Screening Visit. This ID system has the ability to track individual subjects across multiple HSG CTCC studies without storing any personally identifiable information. The protected system uses an algorithm of nine data element inputs (last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, and mother's maiden name), and produces an electronic "fingerprint" output. The system stores only the "fingerprint" and clears the individual's inputted data elements from memory. The subject is then assigned a 9-digit CTCC Unique ID Number that is associated with their electronic "fingerprint."

Once the informed consent/assent, is signed to obtain the CTCC unique ID, the subject (or designee) will be directed to a secure website where he/she or the site Study Coordinator (if the patient requests/prefers) will enter the subject's nine data elements. The CTCC Unique ID Number will be printed and provided to the patient. The Study Coordinator will record this number on the eCRF and Confidential Subject ID Log.

If a patient has participated in previous CTCC studies and already has an existing CTCC Unique ID Number, this number will be used for this study. When the same nine data elements are entered in the exact same way they were entered the first time, the same CTCC Unique ID Number will be generated.

The caregiver will also be asked to review and sign the consent form. Caregivers will not be assigned Subject Identification or Unique ID numbers.

After informed consent/assent has been obtained, and any washout of prohibited medications completed, screening activities will be performed on all suitable subjects within the 4 weeks prior to first dose to determine if subjects meet the inclusion/exclusion criteria.

Subjects switching from tetrabenazine (Switch subjects) will undergo a full screening evaluation within 30 days of the Baseline assessment prior to switching to SD-809 ER. See Schedule of Events A.

The **Switch** Screening clinic visit will consist of the following:

- Evaluate capacity for consent and obtain informed consent/assent
- Assign Subject ID
- Assign Unique ID
- Complete Research Advance Directive, if subject has the capacity to provide informed

consent (See Section 6.12)

- Complete medical history including demographics, concomitant medications (including over the counter, vitamins, and herbal supplements) and alcohol use
- Assessment of chorea control (in consultation with the subject and caregiver)
- Brief physical examination, vital signs, height and weight
- Complete neurological examination
- Clinical laboratory tests:
 - Safety labs: serum chemistry, hematology, prothrombin time and urinalysis
 - Screening labs: virology screen (HBsAg), serum human chorionic gonadotropin (hCG) pregnancy test (women of child-bearing potential only), serum FSH (in order to confirm post-menopausal status).
- Other tests: Blinded CAG repeat
- Blinded CYP2D6 genotype blood sampling
- 12-lead ECG
- Columbia Suicide Severity Rating Scale (C-SSRS): Baseline version
- Unified Huntington's Disease Rating Scale (UHDRS):
 - Motor
 - TFC
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Swallowing Disturbance Questionnaire (SDQ)
- Provide **Switch** subjects with a diary card to record the start time of their last meal and time of their last tetrabenazine dose prior to the Baseline visit and ask them to bring the diary card with them to the next clinic visit.
 - Schedule a telecon one week before the Baseline visit to remind Switch subjects to complete the diary card, and hold dose of tetrabenazine on the day of their Baseline visit if their visit is scheduled in the morning. If the subject is scheduled in the afternoon, subjects will be reminded to take their dose(s) of tetrabenazine as per their usual schedule. Subjects will be reminded to bring their tetrabenazine with them to their Baseline visit.
- Evaluate selection criteria and, if eligible to enroll, schedule Baseline clinic visit
- Order study medication

Abnormal screening labs may be repeated once, without medical monitor approval, to determine the subject's eligibility.

Subjects may be rescreened, with approval of the medical monitor, if they have an abnormal laboratory value or an acute condition preventing them from qualifying for the study if the condition:

- Has resolved or is resolving

- Does not meet the criteria for a Serious Adverse Event
- Is not expected to interfere with the subject's ability to complete the study as designed, in the opinion of the investigator.

Screening results will be assessed by the Investigator or Sub-Investigator and subjects who meet selection criteria will be considered for enrollment into the study.

6.1.2 Prior Data from Study SD-809-C-15 (Rollover Subjects)

See Schedule of Events B for data to be imported from SD-809-C-15 after Informed Consent.

Subjects who have successfully completed Study SD-809-C-15 may be eligible to rollover directly into this study after they complete a one week washout and the Week 13 (visit window up to 10 days) evaluation of Study SD-809-C-15. To reduce subject burden, after obtaining capacity assessment (if applicable)/informed consent/assent and Research Advance Directive (if applicable), some data collected in the SD-809-C-15 study will be utilized in the SD-809-C-16 study and provide some of the baseline data for SD-809-C-16 (See Schedule of Events B). In addition to assessments completed for the SD-809-C-15 Week 13 visit, evaluations required as part of the SD-809-C-16 study will be completed on the same day as the Week 13 visit. All subjects are expected to rollover to SD-809-C-16 at the Week 13 visit of SD-809-C-15.

Baseline visit study drug will be shipped after site's approval to receive study drug. See Operations Manual for further details.

6.1.3 Baseline Visit (Day 0)

See the Schedule of Events A and B for a detailed summary of activities.

Subjects will return to the clinic on Day 0 to undergo baseline evaluation. Subjects who continue to meet selection criteria will be enrolled in the study.

Subjects switching from tetrabenazine (Switch subjects)

Subjects will be converted from their TBZ regimen to an SD-809 ER regimen that is predicted to provide comparable exposure to total (α + β)-dihydrotrabenazine (α - and β -HTBZ). Subjects will continue taking their TBZ regimen through midnight of Day 0 and then directly switch to their assigned SD-809 ER regimen the next morning.

The **Switch** Baseline clinic visit will consist of the following:

Note: The italicized procedures listed immediately below should be done before PK blood sampling to assure the subject still qualifies for study participation:

- *Adverse events and concomitant medication use*
- *Collect and review diary card*
- *Urine pregnancy test (women of child-bearing potential only)*
- *Hospital Anxiety and Depression Scale (HADS)*
- *Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version*
- *Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item*
- *Swallowing Disturbance Questionnaire (SDQ)*

- *Physical examination, vital signs (including orthostatic blood pressure and pulse) and weight*
- *Baseline results will be assessed by the Investigator or Sub-Investigator and subjects who meet eligibility criteria will be enrolled into the study.*
- Clinical laboratory tests: serum chemistry, hematology, and urinalysis
- PK blood sampling for tetrabenazine (See Section 6.8)
- Administer tetrabenazine post pre-dose sampling (Switch subjects scheduled for morning visits only)
- Montreal Cognitive Assessment (MoCA[®])
- Complete Unified Huntington's Disease Rating Scale (UHDRS):
 - Motor
 - Cognitive
 - Behavior
 - Functional assessment
 - Independence
 - TFC
 - Summary
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Subjects will be provided with one week of study medication.
- Week 1 clinic visit will be scheduled.

Subjects from the SD-809-C-15 Study (Rollover subjects)

Subjects who have successfully completed Study SD-809-C-15 may be eligible to rollover directly into this study after they complete the Week 13 evaluation of Study SD-809-C-15. To reduce subject burden, after obtaining capacity assessment (if necessary)/informed consent/assent and Research Advance Directive (if applicable), some data collected in the SD-809-C-15 study will be utilized in the SD-809-C-16 study and will provide some of the baseline data for SD-809-C-16 (See Schedule of Events B). Additional evaluations required as part of the SD-809-C-16 study will be completed on the same day as the Week 13 visit of the SD-809-C-15 study after SD-809-C-16 informed consent/assent is provided. All subjects are expected to rollover to SD-809-C-16 at the Week 13 visit of SD-809-C-15. See Schedule of Events B.

Prior to conduct of any study-specific screening procedures, the Investigator, or designee, will explain to the subject and caregiver the study procedures, including the risks involved and the fact that their participation is voluntary. If subject lacks the capacity to provide informed consent (as determined by an independent assessment by a qualified healthcare provider not directly involved in other study activities), a legally authorized representative must provide written informed consent and the subject must provide assent. Each subject and caregiver will acknowledge receipt of this information by signing and dating a current, IRB/IEC-approved

written informed consent, or subject assent if an LAR is utilized, for their involvement in the study in the presence of the Investigator, or designee, who will also sign and date the informed consent or assent.

The **Rollover** Baseline clinic visit will consist of the following:

- Evaluate capacity for consent and obtain informed consent/assent (for subjects who do not already have a legally authorized representative)
- Complete Research Advance Directive, if subject has the capacity to provide informed consent (See Section 6.12)
- Update medical history
- Urine pregnancy test (women of child-bearing potential only)
- Montreal Cognitive Assessment (MoCA[®])
- Unified Huntington's Disease Rating Scale (UHDRS)
 - Cognitive
 - Behavior
- Baseline results will be assessed by the Investigator or Sub-Investigator and subjects who meet eligibility criteria will be enrolled into the study.
- Subjects will be provided with one week of study medication
- Week 1 telephone visit will be scheduled

6.2 *Dose Adjustment/Titration Period*

All subjects will interact weekly with the clinical site, either by telephone contact or clinic visit, during the dose adjustment/titration period, in order to evaluate safety and establish a dose of study drug that adequately controls chorea and is well-tolerated. Safety evaluations include UHDRS motor examination, laboratory testing, ECGs, monitoring for adverse events and rating scales for depression, cognitive function, akathisia, swallowing disturbance and somnolence. Subjects on allowed doses of citalopram (Celexa) or escitalopram (Lexapro, Cipralext) will have additional ECGs during the titration period as specified in the Schedule of Events.

For subjects switching from tetrabenazine (Switch subjects) the dose of SD-809 ER may be adjusted weekly (upward or downward) in increments of 6 mg per day (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached) until a dose level that adequately controls chorea is identified, the subject experiences a protocol defined "clinically significant" adverse event (defined as related to study medication and either a) moderate or severe in intensity or b) meets the criteria for a Serious Adverse Event [SAE]¹; or the maximal allowable dose is reached. If a subject experiences a "clinically significant" AE attributable to SD-809 ER, the investigator will determine if a dose reduction or suspension is necessary. The investigator, in consultation with the subject and caregiver, will determine when an adequate level of chorea control has been achieved. Subjects will have a clinic visit at Week 1 and a telephone contact at Week 2, in order to evaluate safety and establish an optimal dose. Although subjects will enter the long term

¹ See Section 7 for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

treatment period after Week 2, dose adjustment (upward or downward) may continue through Week 4 to optimize dose level. Additional dose adjustments may be made after Week 4 if clinically indicated.

As all subjects from the SD-809-C-15 Study (Rollover subjects) will have discontinued study drug (SD-809 ER or placebo) for 1 week after completion of the SD-809-C-15 study, they will undergo titration on SD-809 ER. During titration, the investigator, in consultation with the subject and caregiver, will determine when an adequate level of chorea control has been achieved. The dose of SD-809 ER may be adjusted on a weekly basis (upward or downward), in increments of 6 mg per day (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached), until there is adequate control of chorea; the subject experiences a protocol defined “clinically significant” adverse event (defined as related to study medication and either a) moderate or severe in intensity or b) meets the criteria for a Serious Adverse Event [SAE]); or the maximal allowable dose is reached. If a subject experiences a “clinically significant” AE attributable to SD-809 ER, the investigator will determine if a dose reduction or suspension is necessary. Subjects will have a telephone contact at Week 1 and a clinic visit at Week 2, in order to evaluate safety and establish a dose of study drug that adequately controls chorea and is well-tolerated. Although subjects will enter the Long term treatment period after Week 2, titration may continue through Week 8 to optimize dose level. Additional dose adjustments may be made after Week 8 if clinically indicated.

Once adequate control of chorea has been achieved or the maximum allowable dose has been reached, the dose of SD-809 ER should not be increased further.

If a subject experiences an AE that is attributed to study drug, the investigator will use his or her judgment to determine if a dose reduction or suspension is necessary. Dose adjustments should be made based on all available information including the subject’s and caregiver’s reports of adverse events and chorea control, the clinical assessment of safety and efficacy by the investigator, and information from rating scales such as the UHDRS, the HADS, the UPDRS (dysarthria item), the Barnes Akathisia Rating Scale, the Epworth sleepiness scale, and the C-SSRS. At the end of the dose adjustment/titration period, the subject’s dose will be established for the remainder of the long term treatment period.

6.2.1 Switch Subjects - Weeks 1 and 2

See the Schedule of Events A for a detailed summary of activities.

Switch subjects will have a clinic visit at Week 1 and a telephone contact at Week 2 for evaluation of safety and SD-809 ER dose level.

The **Switch Week 1 clinic visit** will include the following activities:

- Assessment of adverse events, chorea control (in consultation with the subject and caregiver), and concomitant medication use
- Vital signs
- Weight
- For subjects on allowed doses of citalopram (Celexa) or escitalopram (Lexapro, Ciprallex): Perform a 12-lead ECG
- Hospital Anxiety and Depression Scale (HADS)

- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Unified Huntington's Disease Rating Scale (UHDRS)
 - Motor
 - Behavior
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Swallowing Disturbance Questionnaire (SDQ)
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Evaluation of SD-809 ER dose level and adjustment, if necessary, based on subject's reports of adverse events and chorea control (in consultation with the subject and caregiver), clinical assessment of safety and efficacy, and information from the above rating scales.
- Assessment of medication accountability/compliance
- Re-order study medication
- The Week 2 telephone contact will be scheduled/reconfirmed

The **Switch Week 2 telephone contact** assessments will include:

- Assessment of adverse events, chorea control (in consultation with the subject and caregiver) and concomitant medication use
- Evaluation of study drug dose level and adjustment, if necessary
- Re-order study medication (See Operations Manual for further details)
- Next telephone contact will be scheduled/reconfirmed

6.2.2 Rollover Subjects - Weeks 1 and 2

See the Schedule of Events B for a detailed summary of activities.

Rollover subjects will have a telephone contact at Week 1 and clinic visit at Week 2 of the study for evaluation of safety and SD-809 ER dose level.

The **Rollover Week 1 telephone contact** will include the following activities:

- Assessment of adverse events, chorea control (in consultation with the subject and caregiver) and concomitant medication use
- Evaluation of study drug dose level and adjustment, if necessary
- Re-order study medication
- Next clinic visit will be scheduled/reconfirmed

The **Rollover Week 2 clinic visit** will include the following activities:

- Assessment of adverse events, chorea control (in consultation with the subject and caregiver), and concomitant medication use

- Vital signs
- Weight
- For subjects on allowed doses of citalopram (Celexa) or escitalopram (Lexapro, Cipralex): Perform a 12-lead ECG
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Unified Huntington's Disease Rating Scale (UHDRS)
 - Motor
 - Behavior
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Swallowing Disturbance Questionnaire (SDQ)
- Assessment of medication accountability/compliance
- Evaluation of SD-809 ER dose level and adjustment, if necessary, based on subject's reports of adverse events and chorea control (in consultation with the subject and caregiver), clinical assessment of safety and efficacy, and information from the above rating scales.
- Re-order study medication (See Operations Manual for further details)
- The next telephone contact will be scheduled/reconfirmed.

6.3 Long Term Treatment Period

All subjects will enter the long term treatment period after Week 2, although dose adjustment may continue in Switch subjects and titration may continue in Rollover subjects.

During long term treatment, all subjects will be contacted by telephone at Week 3 and will return to the clinic on Weeks 4, 8, 15, 28 and every 13 weeks thereafter for evaluation of safety and chorea control. In addition, Rollover subjects will have an additional telephone contact at Week 5. Switch subjects will have an additional telephone contact at Week 7, to remind subjects to complete diary card before the Week 8 visit. **Subjects who have not achieved a dose level that adequately controls chorea and is well tolerated by the Week 4 visit (Switch subjects) or Week 5 telecon (Rollover subjects) should have unscheduled visits or telephone contacts in order to further adjust their dose upward or downward.** Site interactions for dose adjustment should alternate between telephone contacts and clinic visits. During long-term treatment, further dose adjustments of SD-809 ER may be made, if necessary, but not more often than weekly and in increments of 6 mg (6 mg/day or 12 mg/day after a total daily dose of 48 mg is reached). Dose adjustments should be based on all available information including the subject's and caregiver's reports of adverse events and chorea control, information from rating scales and all safety evaluations. If subjects become non-ambulatory or require more aid than an assistive device during long term treatment, they will be permitted to remain in the study.

At the end of the long term treatment period, subjects will undergo a comprehensive evaluation, including physical and complete neurological exam, safety labs and 12-lead ECG and performance of all rating scales.

6.3.1 Telephone Contacts (One week prior to Baseline visit [Switch only]; Week 3 ± 3 days [All Subjects]; Week 5 ± 3 days [Rollover only]; Week 7±3 days [Switch only])

See the Schedule of Events A and B for a detailed summary of activities.

All subjects will be contacted by telephone during Week 3 to assess adverse events, chorea control (in consultation with the subject and caregiver), concomitant medication use, evaluation of study drug dose level and adjustment, if necessary and to schedule/confirm the next visit. Following the above assessments, study medication will be re-ordered according to specified procedures.

Rollover subjects will have an additional telephone contact at Week 5 with the same activities.

Switch subjects will have additional telephone contacts one week prior to their Baseline visit and at Week 7 to remind them to complete the diary card and to take or hold the morning dose on the day of their Baseline and Week 8 visits as per their assigned cohort (Rich or Sparse) dosing requirements. In addition, subjects will be reminded to return diary cards at the Baseline and Week 8 visits.

6.3.2 Clinic Visits (Weeks 4, 8, 15, 28 and every 13 weeks thereafter [all ± 3 days])

See the Schedule of Events A and B for a detailed summary of activities.

Long term treatment period clinic visits includes the following activities:

- Assessment of adverse events, chorea control (in consultation with the subject and caregiver) and concomitant medication use
- Brief physical examination (Week 28)
- Weight
- Vital signs (at Week 8, include orthostatic blood pressure and pulse)
- At Week 4, provide **Switch** subjects with a diary card to record the start time of their last meal and the time of their last dose prior to the Week 8 visit and ask them to bring the diary with them to the next clinic visit.
- Collect and review diary card (Week 8 **Switch** subjects only)
- For subjects on allowed doses of citalopram (Celexa) or escitalopram (Lexapro, Cipralext): Perform a 12-lead ECG if the dose of study drug has been increased since the last ECG was collected (Week 4)
- 12-lead ECG (Week 8)
- Clinical laboratory tests: serum chemistry, hematology, and urinalysis (Weeks 8 and 28, and every 26 weeks after Week 28)
- Urine pregnancy test (women of child-bearing potential only)(Week 28 and every 26 weeks thereafter)

- Blood sampling for PK (Week 8, **Switch** subjects only) for SD-809 ER
- Administer SD-809 post PK sample (Switch subjects scheduled for morning visits only)
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Montreal Cognitive Assessment (MoCA[®])
- Unified Huntington's Disease Rating Scale (UHDRS)
 - Motor
 - Cognitive
 - Behavior
 - Functional assessment (Week 28)
 - Independence (Week 28)
 - TFC (Week 28 and every 52 weeks thereafter)
 - Summary (Week 28)
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Swallowing Disturbance Questionnaire (SDQ)
- Assessment of medication accountability/compliance
- Evaluation of study drug dose level and adjustment, if necessary (through Week 4 for **Switch** subjects; through Week 8 for **Rollover** subjects)
- Re-order study medication (See Operations Manual for further details)
- Next clinic visit and telephone contact (Week 4 **Rollover** subjects only) will be scheduled/reconfirmed

Subjects switching from tetrabenazine (Switch subjects) should continue to receive their long term treatment dose after the Week 4 clinic visit, although further dose adjustments are permitted if clinically indicated.

Subjects from the SD-809-C-15 Study (Rollover subjects) should continue to receive their long term treatment dose after the Week 8 clinic visit, although further dose adjustments are permitted if clinically indicated.

Note (**Switch** subjects only): If a subject requires a dose change at Week 8, the Week 8 assessments should be conducted except for PK sampling which should be postponed until Week 15.

6.3.3 Clinic Visit (End of Treatment ± 3 days or Early Termination)

See the Schedule of Events A and B for a detailed summary of activities.

All subjects will stop study drug at the End of Treatment visit. Subjects will return to the clinic

for the following End of Treatment/ET end-of-long term treatment period assessments:

- Assessment of adverse events, chorea control (in consultation with the subject and caregiver) and concomitant medication use
- Physical examination, vital signs (including orthostatic blood pressure and pulse), and weight
- Complete neurological examination
- Clinical laboratory tests: serum chemistry, hematology, urinalysis, and urine pregnancy test (women of child-bearing potential only)
- 12-lead ECG
- Single PK Blood Sample (for Early Termination Visits, if within 48 hours of last dose, if possible)
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Montreal Cognitive Assessment (MoCA[®])
- Unified Huntington's Disease Rating Scale (UHDRS)
 - Motor
 - Cognitive
 - Behavior
 - Functional assessment
 - Independence
 - TFC
 - Summary
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Swallowing Disturbance Questionnaire (SDQ)
- Assessment of medication accountability/compliance and collection of all study medication
- The next clinic visit will be scheduled/reconfirmed

Note: If the subject discontinues from the study early, every effort should be made to complete the early termination procedures as outlined above and in Schedule of Events A and B. In addition, subjects discontinuing prematurely from the study should have a follow up visit 1 week after discontinuing therapy and a follow up telephone contact 4 weeks after discontinuing therapy, if possible. The procedures outlined in Section 6.4 should be followed.

6.4 Post-Treatment Safety Follow Up

Following discontinuation of study medication, subjects will have a clinic visit one week after the last dose for evaluation of safety, chorea and motor function and a telephone contact four weeks after the last dose for review of adverse events and concomitant medication use. During the first week after stopping study drug, subjects should not take prohibited concomitant medications. Between the one-week and four-week post-treatment follow up visits, concomitant medication use is per the discretion of the investigator.

6.4.1 Clinic Visit (1-week follow up \pm 3 days)

See the Schedule of Events A and B for a detailed summary of activities.

All subjects will return one week after the End of Treatment, or Early Termination visit, for evaluation of safety, chorea and motor function. The following activities should be performed:

- Assessment of adverse events, chorea control (in consultation with the subject and caregiver) and concomitant medication use
- Vital signs
- Weight
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Montreal Cognitive Assessment (MoCA[®])
- Unified Huntington's Disease Rating Scale (UHDRS)
 - Motor
 - Cognitive
 - Behavior
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Swallowing Disturbance Questionnaire (SDQ)
- Next telephone contact will be scheduled/reconfirmed

6.4.2 Telephone Contact (4-week follow up \pm 3 days)

All subjects will have a follow up telephone contact four weeks after their last dose of study medication. During the telephone contact, subjects and caregivers will be questioned about adverse events and concomitant medication use since the subject's last evaluation.

6.5 Unscheduled Visit(s)

See the Schedule of Events A and B for a detailed summary of activities.

Unscheduled visits may be performed for Dose Adjustment or evaluation of intercurrent events. Visits for Dose adjustment should focus on evaluating chorea control, adverse events

and adjusting the dose of study medication, if indicated. Additional safety measures may be performed at the investigator's discretion.

For unscheduled clinic visit(s) conducted during the course of the study, the following activities should be performed:

- Assessment of adverse events, chorea control (in consultation with the subject and caregiver), and concomitant medications
- Vital signs and weight
- Unified Huntington's Disease Rating Scale (UHDRS)
 - Motor
- Evaluation of study drug dose level and adjustment, if necessary

The following assessments are at the Investigator's discretion and should be performed if indicated:

- 12-lead ECG
- Clinical laboratory tests: serum chemistry, hematology, and urinalysis
- Single PK Blood Sample (for Unscheduled Visits due to SAE, if within 48 hours, if possible)
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Swallowing Disturbance Questionnaire (SDQ)

- Re-order study medication

For unscheduled telephone visit(s) needed during the course of the study, the following activities should be performed:

- Assessment of adverse events, chorea control and concomitant medications in consultation with the subject and caregiver.
- Evaluation of study drug dose level and adjustment, if necessary (at the Investigator's discretion)

- Re-order study medication (at the Investigator's discretion) (See Operations Manual for further details)

6.6 Safety Evaluations

6.6.1 Demographics and Medical History

The subject's gender, date of birth, race, ethnic origin, and medical and surgical history will be obtained at Screening for C-16 Switch subjects and recorded in the electronic Case Report Form (eCRF) and transferred from data collected in C-15 for Rollover subjects. The subject's medical and surgical history will be updated at Baseline for C-16 Rollover subjects.

6.6.2 Physical Examination

A complete physical examination will be performed as specified in the [SCHEDULE OF EVENTS A – SUBJECTS SWITCHING FROM TETRABENAZINE](#) or [SCHEDULE OF EVENTS B – SUBJECTS ROLLING OVER FROM SD-809-C-15](#). A complete examination includes evaluation of the following systems/regions:

<ul style="list-style-type: none">• General Appearance• Skin• Head, Eyes, Ears, Nose, Throat• Neck: Lymph Nodes, pulses• Cardiovascular*	<ul style="list-style-type: none">• Respiratory*• Musculoskeletal• Abdominal*• Extremities
--	---

* Systems evaluated in brief physical examination

A **brief physical** examination includes evaluation of the cardiovascular, respiratory, and abdominal systems.

6.6.3 Complete Neurological Examination

A complete neurological examination will be performed as specified in the [SCHEDULE OF EVENTS A – SUBJECTS SWITCHING FROM TETRABENAZINE](#) or [SCHEDULE OF EVENTS B – SUBJECTS ROLLING OVER FROM SD-809-C-15](#). The neurological examination includes evaluation of the following:

<ul style="list-style-type: none">• Mental status• Cranial nerves• Motor system (strength, tone posture)• Coordination	<ul style="list-style-type: none">• Gait and balance• Tendon reflexes• Sensation
---	--

6.6.4 Vital Signs

Vital signs to be assessed should include resting blood pressure, heart rate, respiratory rate, and temperature. Heart rate and blood pressure measurements should be taken only after a subject has rested quietly in a sitting position for at least 5 minutes.

6.6.5 Orthostatic Blood Pressure and Pulse

Orthostatic blood pressure and pulse will be recorded at Baseline, Week 8 and End of Treatment/ET.

Orthostatic blood pressure and pulse will be assessed in the supine and standing positions. The subject should be supine for at least 5 minutes before the supine blood pressure and pulse are measured. Subjects will then move to the sitting position briefly to assure no symptoms occur after which they will stand for 3 minutes. Standing blood pressure and pulse will be obtained after the subject has been in the standing position for at least 3 minutes.

6.6.6 Laboratory Tests

Blood and urine samples will be collected and analyzed, and applicable parameters calculated according to the Standard Operating Procedures (SOPs) at the central laboratory. If abnormal, screening labs may be repeated once to confirm the subject's eligibility.

<i>Serum Chemistry</i>		
<ul style="list-style-type: none"> • Sodium • Potassium • Chloride • Bicarbonate • Magnesium • Glucose • Blood urea nitrogen (BUN) 	<ul style="list-style-type: none"> • Creatinine • Total calcium • Phosphate • Uric Acid • Cholesterol • Triglycerides • Total Protein 	<ul style="list-style-type: none"> • Albumin • Total bilirubin • Direct bilirubin • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate transaminase (AST) • Lactate dehydrogenase (LDH)

<i>Hematology</i>	<i>Urinalysis</i>
<ul style="list-style-type: none"> • Hemoglobin • Hematocrit • Red blood cell count (RBC) • Mean cell volume (MCV) • Platelets • White cell count • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils 	<ul style="list-style-type: none"> • Leucocytes • Nitrites • Urobilinogen • Protein • pH • Blood • Specific gravity • Ketone • Bilirubin • Glucose • Microscopic exam (if indicated)

<i>Screening Labs</i>	<i>Other</i>
<ul style="list-style-type: none"> • Urine and serum pregnancy tests (women of childbearing potential only) • Follicle Stimulating Hormone (FSH) for post-menopausal women only. • Hepatitis B surface antigen (HBsAg) 	<ul style="list-style-type: none"> • CYP2D6 genotype (blinded) • CAG repeat (blinded) • Prothrombin Time (PT) International Normalized Ratio (INR)

6.6.7 12-lead Electrocardiogram (ECG)

All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.

12-lead ECGs to assess safety will be recorded according to the [SCHEDULE OF EVENTS A – SUBJECTS SWITCHING FROM TETRABENAZINE](#) or [SCHEDULE OF EVENTS B –](#)

SUBJECTS ROLLING OVER FROM SD-809-C-15 and interpreted by a cardiologist. Heart rate and ECG intervals (PR, QRS, QT, and QTcF) and clinical interpretation will be assessed by the cardiologist and recorded in the CRF.

6.6.8 Detecting Adverse Events

The occurrence of adverse events (AEs) should be sought by non-leading questioning of the subject and caregiver during the study and may also be identified when the subject and/or caregiver spontaneously volunteered them. Open-ended, non-leading questioning of the subject is the preferred method to detect AEs.

Suitable non-leading questions include:

- “How are you feeling?”
- “How have you been doing since your last evaluation?”
- “Have you taken any new medicines since your last evaluation? If so, why?”

Adverse events may also be detected by the medical staff through physical examination, evaluation of laboratory tests results or other assessments. All adverse events occurring from signing of the ICF to the end of the study, regardless of suspected causal relationship to study drug, will be recorded in the source documentation and on the appropriate eCRF page for subjects who are enrolled.

6.7 Rating Scales

Subject completed assessments will be available in English, Spanish and French.

6.7.1 Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-administered instrument reliable for detecting states of depression and anxiety in an outpatient medical setting (14). The HADS is recommended by the National Institute of Neurological Disorders & Stroke (NINDS) Common Data Elements for Huntington Disease because it serves as a good screening measure, it has been widely used and it is relatively simple to complete. It focuses on subjective disturbances of mood rather than physical signs, and aims at distinguishing depression from anxiety. The scale consists of 14 items (7 each for anxiety and depression). Each item is rated on a four point scale ranging from 0 (not at all) to 3 (very often). Responses are based on the relative frequency of symptoms over the preceding week.

6.7.2 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is an FDA endorsed questionnaire to screen for suicidality in trials of central nervous system (CNS) active compounds (15, 16). The C-SSRS is an interview by trained study personnel that should be done at Baseline and during the study as outlined in the Schedule of Events. The form provided at Screening collects the history of suicide (C-SSRS form version termed “baseline”) and subsequent visits use a C-SSRS termed “Since the Last Visit”.

6.7.3 Unified Huntington’s Disease Rating Scale (UHDRS)

The UHDRS is a research tool which has been developed by the HSG to provide a uniform assessment of the clinical features and course of HD (17). As the authors sought to develop a

tool for evaluating interventions that modify disease progression, they suggested the UHDRS may be suitable for tracking longitudinal changes. The instrument was not intended to assess the impact of short-term treatment effects, although it has often been used for such purposes. The components of the UHDRS are:

- Motor Assessment
- Cognitive Assessment
- Behavioral Assessment
- Independence Scale
- Functional Assessment
- Total Functional Capacity (TFC)

6.7.4 Montreal Cognitive Assessment (MoCA[®])

The Montreal Cognitive Assessment (MoCA[®]) is a validated rapid screening instrument for assessing mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA[®] is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal. There are 3 versions in the English language. Given the relatively frequent use of this instrument, the versions will be rotated at each visit. Additionally, Spanish and French language versions may be utilized.

6.7.5 Unified Parkinson's Disease Rating Scale (UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS) is a comprehensive instrument used to assess the signs and symptoms of Parkinson's disease. The UPDRS is comprised of various patient and clinician based assessments of motor, cognitive, and behavioral symptoms. UPDRS questions pertaining to dysarthria will be utilized to screen and monitor study subjects for parkinsonism.

6.7.6 Barnes Akathisia Rating Scale (BARS)

The Barnes Akathisia Rating Scale (BARS) is a widely used rating scale for evaluation of drug induced akathisia. This scale includes an objective assessment, subjective measures, including self-awareness and distress, and a global clinical assessment (18).

6.7.7 Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire comprised of eight questions that provides a measure of a subject's general level of daytime sleepiness (19). The ESS asks respondents to rate, on a 4-point Likert scale (0 – 3), their usual chances of dozing off or falling asleep in different situations or activities that most people engage in as part of their daily lives. The total ESS score is the sum of 8 item-scores and can range between 0 and 24 with a higher the score indicating a higher level of daytime sleepiness. Most people can complete the ESS, without assistance, in 2 or 3 minutes.

6.7.8 Swallowing Disturbance Questionnaire (SDQ)

The Swallowing Disturbance Questionnaire is a self-administered questionnaire comprised of 15 questions that assess frequency of swallowing disturbance (20). It has been validated in subjects with Parkinson’s disease and has been shown to be a sensitive and accurate tool for identifying subjects with swallowing disturbances arising from different etiologies. A sensitivity and specificity analysis demonstrated that a threshold score of 11 was the optimal score for identifying subjects with dysphagia that had underlying pathology confirmed on fiberoptic endoscopic evaluation of swallowing (FEES) (21).

6.8 Pharmacokinetic Evaluations

A pharmacokinetic (PK) sub-study will be conducted in **subjects switching** from TBZ to SD-809 ER. Blood samples will be obtained for measurement of plasma concentrations of SD-809, tetrabenazine and their respective α HTBZ, β -HTBZ, total ($\alpha+\beta$)-HTBZ and other metabolites, as required. Approximately one third of the population will have rich samples drawn and the remaining two thirds will have sparse sampling. The rich sampling cohort should be enrolled first. Subjects who are unable or unwilling to participate in the rich sampling cohort may be assigned to the sparse sampling cohort.

Subjects in the rich sampling cohort must have a morning visit in which the AM dose of tetrabenazine or SD-809 ER is administered in clinic. If the subject is assigned to the rich group at the Screening Visit but forgets to hold tetrabenazine dose the morning of the Baseline visit, the subject must be re-consented to undergo sparse sampling. Subjects in the sparse sampling cohort may have a morning or an afternoon visit. If sparse sample subjects have a morning visit, the AM dose of tetrabenazine or SD-809 ER should be administered in clinic as with the rich sampling cohort. If sparse sampling subjects have an afternoon visit, tetrabenazine or SD-809 ER should be taken at home per their usual schedule. Blood samples will be collected at Baseline (on tetrabenazine) and at Week 8 (on SD-809 ER) as follows:

Cohort	Visit	Day 0 (TBZ)	Week 8* (SD-809 ER)
Rich Sampling (N=12)	Morning only	Pre-dose, 0.5, 1, 2 and 6 hours post-dose	Pre-dose, 1.5, 2.5, 4 and 6 hours post-dose
Sparse Sampling (N=24)	Morning	Pre-dose and 1-2 hours post-dose	Pre-dose and 2-4 hours post-dose
	Afternoon	1 st sample during the visit and 2 nd at least 1 hr† afterward	1 st sample during the visit and 2 nd at least 2 hrs† afterward

* If a subject requires a dose change at Week 8, the Week 8 visit assessments should be conducted except for PK sampling which should be postponed until Week 15.

† The second PK sample for sparse sampling (afternoon) should be taken as late as possible during the visit.

Subjects in the rich sampling cohort and those in the sparse sampling cohort who have a morning visit should be reminded not to take their morning dose at home prior to their Baseline visit (tetrabenazine) and prior to their Week 8 visit (SD-809 ER) as it will be administered in clinic. Morning clinic visits should be scheduled early in the day to allow sufficient time for PK blood sampling.

Samples should be collected as close to the target time as possible. The pre-dose specimen should be taken within one hour prior to drug administration. The actual sample collection time will be recorded in the source document worksheets.

At each time point, four (4) mL of blood will be collected into lithium heparin tubes and processed to plasma. After centrifugation, the plasma will be split into 2 aliquots and stored frozen in polypropylene plasma storage tubes at -70°C or below. If a subject requires a dose change at Week 8, the Week 8 visit assessments should be conducted except for PK sampling which should be postponed until Week 15.

Switch subjects will be provided with a diary at the Screening and Week 4 visits to record meal and dosing times before PK sampling at Baseline and Week 8. Prior to clinic visits subjects will be reminded to record the start time of their last meal and the time of their last dose in their diary card and to bring the diary card with them to the clinic visit. **Switch subjects will be reminded to bring their tetrabenazine to the Baseline visit and the SD-809 ER to the Week 8 visit.**

Subjects who withdraw early from the study should have a single blood sample collected for PK at the Early Termination Visit if the last dose was within the prior 48 hours, if possible.

Subjects experiencing an SAE should have a single blood sample collected as soon as possible after the SAE and within 48 hours for the pharmacokinetics of α - and β - HTBZ, if possible. The date and time of the last dose of study medication should be recorded along with the date and time of the sample collection.

6.9 Subject Restrictions

6.9.1 Concomitant Medications

The following products should not be used within 4 weeks of Screening or Baseline and throughout the study:

- Antipsychotics (See [Appendix 13](#))
- Metoclopramide
- MAO Inhibitors
- Levodopa or dopamine agonists
- Reserpine
- Amantadine
- Memantine (Rollover subjects only)
 - Switch subjects may receive Memantine if on a stable, approved dose for at least 30 days.

Subjects discontinuing anti-psychotics (See [Appendix 13](#)) or the other concomitant medications noted above in order to enroll in the trial must be stable off therapy for at least 30 days before Screening.

Subjects receiving antidepressant therapy must be on a stable dose for 8 weeks before Screening. Additionally, subjects switching or discontinuing SSRIs in order to enter the trial, must be stable on their new regimen for at least 8 weeks before Screening.

The drugs listed above and other drugs which are known to cause QT prolongation (See [Appendix 12](#)) should not be taken concomitantly with study medication. A washout period of 5 half-lives is recommended or other duration as approved by the Clinical Monitor.

Female subjects on hormonal contraception (approved oral, transdermal, or depot regimen) for birth control must be on a stable dose for at least 3 months prior to Screening and through study completion.

Subjects will be instructed to inform the study Investigator of the details (indication, dose, and dates of administration) if they do take any medication, and these details will be recorded in the eCRF.

6.9.2 Use of Alcohol or Sedating drugs

As with other VMAT2 inhibitors (tetrabenazine, reserpine), subjects should be advised that the concomitant use of alcohol or other sedating drugs with SD-809 ER may have additive effects and cause or worsen somnolence. Until subjects are receiving a stable dose of SD-809 ER and understand how the drug affects them, alcohol should be used with caution.

6.9.3 Other Restrictions

Subjects should be advised to not drive a car or operate dangerous machinery until they understand how SD-809 ER affects them.

Use of illicit drugs is prohibited from the time of signing of the Informed Consent Form or Assent and throughout study participation.

6.10 Caregiver Responsibilities

Each subject participating in the study must have a reliable caregiver. The caregiver must interact on a daily basis with the subject and oversee study drug administration. In addition, the caregiver will assure attendance at study visits and participate in evaluations, as required. Note:

- Subjects with a TFC score of 5-7 at Screening must have a live-in caregiver.
- Subjects with a TFC score of 5-7 at Screening or those who enrolled with the consent of an LAR, must have caregivers present at all study visits.
- For subjects with a TFC score of 8-13 at Screening who did not require an LAR to provide informed consent, the caregiver must attend the following visits: Screening, Baseline, Weeks 4, 8, 15, 28 and visits every 13 weeks thereafter through the end of the Long Term Treatment Period. Caregivers will be encouraged to attend other visits.

The caregiver must also make him/herself available for telephone contacts in order to report chorea control and adverse events to determine whether dose adjustment of study drug will be made. As subjects may have agnosia to chorea, telephone contacts should involve the subject and caregiver **at the same time**, if possible.

6.11 Capacity Assessment

In order to determine if a subject can provide informed consent to participate in the trial, an assessment of capacity must be made by a qualified healthcare provider who is not directly involved with other aspects of the study (e.g., cannot be the Site Investigator). The qualified individual must be a health care professional with documented training and experience who has an established role for assessing capacity for treatment consent at the institution. A written assessment verifying the subject has the capacity to provide consent must be maintained in the subject's source documentation.

6.12 Research Advance Directive

During the consenting process, subjects who have the capacity to provide informed consent will be required to provide a research advance directive specific for this trial and will expire when the subject completes participation. A research advance directive will specify whether a subject wishes to continue participation in the study should he or she lose capacity. In the event that a subject loses the capacity to provide consent during the course of the trial, it would allow the subject to continue participation, if so expressed (22, 23).

6.13 Withdrawal Criteria

Subjects will be advised that they are free to withdraw from the study at any time for any reason. A subject may be withdrawn from the study for any of the following reasons:

- Subject voluntarily discontinues study participation (subject withdrawal);
- The need to take medication which may interfere with study measurements;
- Intolerable/unacceptable adverse events;
- Major violation or deviation of study protocol procedures;
- Non-compliance of subject with protocol;
- Subject is unable to comply with study procedures;
- Withdrawal from the study is, in the Investigator's judgment, in the subject's best interest;
- Subject is lost to follow-up;
- A female subject becomes pregnant;
- Study termination by the Sponsor.

All Subjects to be withdrawn from the study for medical reasons should be reviewed with the Clinical Monitor. The reasons for withdrawal will be recorded on the eCRF and included in the final report along with any adverse events and any necessary medical treatment.

6.14 Discontinued Subjects

Notification of early subject discontinuation from the study and the reason for discontinuation will be made to the Clinical Monitor and will be clearly documented on the appropriate eCRF page. If a subject is discontinued from the study early, all early termination evaluations should be performed at the time of discontinuation, if possible.

6.15 Study Termination

The study may be stopped at any time by the Sponsor, IEC/IRB, and/or regulatory agencies for any reason. The Sponsor reserves the right to discontinue the trial at any time for any reason. Reasons will be provided in the event of this happening. The Investigator reserves the right to discontinue the study for safety reasons at any time in collaboration with the Sponsor.

7 ADVERSE EVENTS

Throughout the course of the study, all adverse events will be monitored and reported on an

adverse event case report form, including assessments of seriousness, severity, action taken and relationship to study drug. If adverse events occur, the first concern will be the safety of the study participants.

Adverse events will be recorded from the time of consent through the final study visit.

Information about side effects already known about the investigational product(s) can be found in the Investigator's Brochure (IB) and will be included in the subject informed consent form.

The Investigator and site staff are responsible for detection, recording and reporting of events that meet the criteria and definition of an AE or SAE (listed below).

7.1 Definitions

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) therefore, can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Abnormal safety assessments if they lead to investigational product dose modification, investigational product discontinuation or to therapeutic intervention (e.g. low hemoglobin that requires transfusions).
- Abnormal laboratory tests if they are associated with clinical signs, symptoms or if they lead to a diagnosis or therapeutic intervention.
- Abnormal vital signs if they are clinically significant and lead to a diagnosis or therapeutic intervention.
- Abnormal ECGs if they are clinically significant and lead to therapeutic intervention or diagnosis. The clinical significance should be confirmed by a cardiologist.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication.

Examples of an AE do not include:

- A medical or surgical procedure (e.g. endoscopy); a condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or

convenience admission to hospital) or scheduled elective procedures like cosmetic surgery are not AEs. However, if the procedure results in an unexpected complication, the complication is an AE.

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence did not occur or when signs are not expressing a medical problem but rather are expressing natural physiological responses (e.g., dyspnea after running, limb paresthesias due to awkward position).
- Signs, symptoms, or laboratory results that reflect an improvement of a past medical condition (e.g. sleeping better).

7.1.2 Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Adverse Reaction

An adverse reaction means an adverse event that is caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.1.4 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.5 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death (i.e., the AE caused the death).
- Is life-threatening. The term life threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient overnight hospitalization or prolongation of an existing

hospitalization, unless hospitalization is for:

- Elective or pre-planned treatment for a pre-existing condition and has not worsened since signing the informed consent
- Social reasons and/or respite care in the absence of any deterioration of the subject's general condition.

In general, hospitalization signifies that the subject has been detained (involving at least an overnight stay of at least 24 hours) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious.

- Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect (i.e., an adverse finding in a child or fetus or a subject exposed to the study medication prior to conception or during pregnancy).
- Is medically important, defined as an event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above, or result in urgent investigation. Examples of such events are malignancies, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- If either the Sponsor or Investigator believes the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

7.2 Recording of Adverse Events

Whenever possible, a unifying diagnosis should be recorded in the eCRF as the AE rather than individual signs or symptoms. Similarly, the unifying diagnosis should be recorded as the AE rather than the abnormal laboratory result (i.e. "anemia" instead of "low hemoglobin").

If the AE is a worsening of a past medical condition, the AE should clearly indicate that the past medical condition has worsened using words such as "worsening," "aggravated," or "exacerbation."

7.2.1 Recording of Non-Serious Adverse Events (AEs)

Collection of AEs will begin immediately following signing of the ICF through the final study visit. The Investigator will monitor each subject closely and record all observed or volunteered AEs. Adverse findings detected at the Screening visit (e.g., abnormalities on clinical laboratory testing, ECGs, physical/neuro examination) will be recorded on the Medical History CRF and adverse events occurring after the Screening visit but before starting study treatment will be recorded on the AE CRF and considered non-treatment emergent.

7.2.2 Recording of Serious Adverse Events (SAEs)

Collection of SAEs will begin immediately following signing of the ICF through the final study visit. The Investigator will monitor each subject closely and record all observed or volunteered SAEs. Serious adverse events occurring after signing the informed consent form but before starting study treatment will be considered non-treatment emergent.

If a new SAE comes to the attention of the Investigator after the completion of the final study visit, information regarding the SAE should be collected and reported to the Sponsor only if assessed as reasonably possibly related to the study drug(s) by the Investigator.

After the initial SAE report, the Investigator is required to proactively follow each subject and provide further information to the Sponsor (or designee) on the subject's condition. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

SAEs that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. All SAEs will be followed:

- until resolution, or
- for 28 days after the subject's last follow up visit, or
- if, in the investigator's opinion, the condition is unlikely to resolve, whichever comes first. If the Investigator and Sponsor agree the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

Subjects experiencing an SAE should have a single blood sample collected as soon as possible after the SAE and within 48 hours for the pharmacokinetics of α - and β -HTBZ, if possible. The date and time of the last dose of study medication should be recorded along with the date and time of the sample collection.

7.3 Evaluation of Adverse Events (Serious and Non-Serious)

At each in-person visit and telephone contacts, occurrence of adverse events will be assessed by verbally asking subjects and caregivers if they have had any problems or symptoms since their last visit.

If the subject or caregiver reports an adverse event, the investigator/coordinator will probe further to determine:

- Time of onset and resolution
- Frequency
- Causality/relation to study treatment
- Intensity
- Action taken regarding study drug
- Outcome

7.3.1 Severity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgment. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

- **Mild:** Awareness of sign or symptom that is easily tolerated.
- **Moderate:** Sign or symptom intense enough to interfere with usual activity
- **Severe:** Interferes significantly with ability to do work or usual activity

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in "Definition of a SAE."

7.3.2 Relationship to Study Drug

The Investigator is obligated to assess the relationship between study drug and the occurrence of each AE. The Investigator will use clinical judgment to determine if there is a reasonable possibility that the drug caused the adverse event. The investigator's assessment of the relationship of each AE to study drug will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product should be considered and investigated, if appropriate. The Clinical Monitor's opinion may be sought in those cases in which the Site Investigator is unable to make an independent judgment. The Clinical Monitor may in turn consult with the principal investigator as needed. The following definitions are general guidelines only to help assign grade of attribution:

- **Unrelated:** The Adverse event is **clearly not related** to the investigational drug
- **Unlikely:** The Adverse event is **doubtfully related** to the investigational drug
- **Possible:** The Adverse event **may be related** to the investigational drug
- **Probable:** The Adverse event **is likely related** to the investigational drug
- **Definite:** The Adverse event **is clearly related** to the investigational drug

7.3.3 Action Taken with Study Treatment

Action taken as a result of an adverse event will be recorded on the Adverse Event eCRF as follows:

- No change
- Dose reduced
- Drug Suspended (See Section 5.2.5 for guidance in contacting Clinical Monitor)
- Drug permanently discontinued

7.3.4 Treatment Required

Treatment required as a result of an AE will be recorded in the subject's source documents, and if medication is required, on the Concomitant medications log:

- None

- Medication Required (record on Concomitant Medications eCRF)
- Hospitalization Required
- Other (specify)

If a diagnosis has been entered as an AE, the treatment(s) recorded may represent the treatment(s) given for one or more sign(s) or symptoms(s) (e.g. Naproxen for the AE “fracture”, without recording “pain due to fracture” or “inflammation due to fracture” as separate AEs).

7.3.5 Outcome

Outcome of an adverse event will be recorded on the Adverse Event eCRF as follows:

- Recovered / Resolved
- Recovering / Resolving
- Recovered / Resolved with Sequelae
- Not Recovered / Not Resolving
- Fatal
- Unknown

7.4 Procedures for Reporting Serious Adverse Events

All serious adverse events occurring during study participation must be reported to the Sponsor (or designee) and to the governing Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required by the IRB/IEC, local regulations, and the governing health authorities.

7.4.1 Completion and Transmission of the SAE Report

Once an Investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to the Sponsor (or designee) within 24 hours. The SAE form (provided in the study operations manual) will always be completed as thoroughly as possible with all available details of the event, signed by the Investigator (or designee), and forwarded to the Sponsor (or designee) within the designated time frames. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Sponsor (or designee) of the event and completing the form. The form will be updated when additional information is received.

Whenever possible, the Investigator will provide an assessment of causality at the time of the initial report as described above.

The Sponsor will provide a list of project contacts for SAE receipt. Any event that in the opinion of the Investigator may be of immediate or potential concern for the subject’s health or well-being will be reported to the Sponsor (or designee).

7.4.2 Regulatory Reporting Requirements for SAEs

The Investigator must promptly report all SAEs to the Sponsor in accordance with the procedures describe above. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities

towards the safety of other subjects are met. The Investigator will be responsible for reporting SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) per local regulatory requirements.

The Sponsor (or designee) is responsible for reporting serious adverse events (SAEs) to the relevant regulatory authorities in accordance with local regulations. That is, SAEs which are determined by the Sponsor to be “Unexpected” and classified as “Suspected Adverse Reactions” will be reported in an expedited manner.

7.5 Procedures for Reporting Pregnancy Exposure and Birth Events

The Investigator must promptly report all pregnancies in female study subjects to the Sponsor (or designee) in accordance with the Operations Manual. While the pregnancy itself is not considered to be an AE or SAE, any pregnancy complications should be recorded as AEs or SAEs. Any pregnancy will be followed through its conclusion for observation of any SAEs including congenital anomalies/birth defects.

8 STATISTICAL PROCEDURES AND DATA ANALYSIS

This section describes the statistical analysis strategy and procedures for the study. Summary statistics will be provided by treatment. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. Details of the data analysis will be described in a separate Statistical Analysis Plan.

8.1 Analysis Populations

Safety Population: The safety population will include all subjects who were administered any study drug. Subjects who are assigned a subject number but withdrew prior to dosing will not be included in the safety population. If relevant, details of their participation and reason for withdrawal will be listed separately in the study report.

All summaries of safety endpoints will be summarized descriptively in the Safety Population.

8.2 Demographics and Baseline Data

Demographic information will be presented for each subject. Medical/surgical history data at baseline will be listed, as will physical examination data.

8.3 Safety Analyses

Safety and tolerability will be assessed throughout the study by monitoring the following parameters:

<ul style="list-style-type: none"> • Adverse events (AEs) • Clinical laboratory tests • Physical examination • Vital signs • 12-lead ECGs • Epworth Sleepiness Scale (ESS) 	<ul style="list-style-type: none"> • Columbia Suicide Severity Rating Scale (C-SSRS) • Unified Huntington’s Disease Rating Scale (UHDRS) • Swallowing Disturbance Questionnaire (SDQ) • Unified Parkinson’s Disease Rating Scale (UPDRS), dysarthria item • Barnes Akathisia Rating Scale (BARS) • Hospital Anxiety and Depression Scale (HADS) • Montreal Cognitive Assessment (MoCA©)
--	--

Safety data will be summarized descriptively for the overall population and based on prior treatment [SD-809 ER or placebo (Rollover subjects) or tetrabenazine (Switch subjects)]. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. Descriptive statistics of change-from-baseline for Rollover subjects will utilize the Baseline from Study SD-809-C-15 (C-15 Baseline) and the Baseline from the present study (C-16 Baseline), as appropriate, and will be specified in the Statistical Analysis Plan.

The nature, frequency, and severity of adverse events will be tabulated for all subjects combined and by treatment. Baseline, within study, end of study, and change-from-baseline values for clinical laboratory evaluations and vital signs will be summarized as appropriate.

Treatment-emergent adverse events and laboratory, vital sign, and ECG parameters will be summarized. In addition, change from baseline will be summarized for laboratory and vital sign parameters. Shift tables will be provided for clinical laboratory results. ECG results will be classified as normal and abnormal and summarized.

8.4 *Safety Endpoints*

The following safety endpoints will be assessed:

- Incidence of adverse events (AEs), serious AEs, severe AEs, drug related AEs, AEs leading to withdrawal during the following periods:
 - Overall
 - During titration in Rollover subjects (up to 8 weeks)
 - During dose adjustment in Switch subjects (up to 4 weeks)
 - During long term treatment
- Observed values and changes from baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis)
- Observed values and changes from baseline in vital signs
- Observed values in ECG parameters and abnormal findings
- Number of subjects with on-treatment QTcF values > 450ms, > 480ms, > 500ms
- Observed values and changes in UHDRS, UPDRS (dysarthria), BARS, HADS, ESS, C-SSRS, and MoCA©
- Duration of time to achieve stable doing of SD-809 ER

8.5 *Sample Size*

Because this is an open label safety study, the sample size is not based on statistical considerations.

8.6 Pharmacokinetics

A population pharmacokinetic analysis will be performed using data from all subjects switching from TBZ to SD-809 in this study together with data obtained from subjects in Study SD-809-C-15 to examine the pharmacokinetics of SD-809 and TBZ and to explore the potential effect of various covariates on the pharmacokinetics of SD-809 and TBZ. The population pharmacokinetic analysis will be discussed in detail in a prospective Statistical Analysis Plan.

8.7 Protocol Deviations and Violations

The Investigator is responsible for ensuring that the study is conducted in accordance with the protocol. No modifications to the protocol, other than those that are deemed necessary to protect the safety, rights, or welfare of subjects by the Investigator are to be made without prior, written approval by the Sponsor. The nature and reasons for the protocol deviation will be recorded where appropriate and indicated. The Sponsor must be notified of all protocol deviations. Significant protocol deviations (e.g. inclusion/exclusion criteria) will be reported to the Sponsor and to the IRB/IEC in accordance with its reporting policy.

8.8 Data Recording

Source data will be transcribed onto source document worksheets and will then be entered into an electronic Case Report Form (eCRF). An Electronic Data Capture (EDC) system with eCRFs will be used for this trial. Instructions for eCRF completion will be provided in a separate document. Source data collection and entry into the eCRF will be completed by authorized study site personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study site personnel prior to the study being initiated and before any data is entered into the eCRF system for any study subjects.

8.9 Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of qualified clinical investigators and appropriate study sites, review of protocol procedures with the clinical investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor. The Sponsor (or designee) will review data accuracy and completeness during and after the study, and any discrepancies will be resolved with the clinical investigator or designee as appropriate.

8.10 Data Management

The data will be entered into a validated FDA 21 CFR part 11 compliant database maintained by sponsor or designee. The data management group for the will be responsible for data processing, in accordance with agreed procedures. The Site Investigator will electronically sign and date the appropriate eCRF page when instructed to do so by the study CRA. This signature will indicate that the Site Investigator inspected or reviewed the data in the database, the data queries, and the site notifications, and agrees with the content.

The standard procedures for handling and processing eCRF records will be followed per Good Clinical Practice (GCP) and the Sponsor's (or designee's) Standard Operating Procedures (SOPs).

Complete details of data management will be described in a separate Data Management Plan.

9 ADMINISTRATIVE ISSUES

This protocol is to be conducted in accordance with the applicable Good Clinical Practice regulations and guidelines including the International Conference on Harmonization Guideline on Good Clinical Practice.

The clinical trial will be conducted in accordance with the applicable regulations of the local regulatory authority.

9.1 Investigator Obligations

9.1.1 Independent Ethics Committee (IEC)/Institutional Review Board (IRB) Approval

Prior to initiation of the study, the written IEC/IRB approval of the protocol and Study Information Forms/Informed Consent Forms based on the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) will be received. This approval will be typed on the Institutional letterhead and will refer to the Study Information Forms/Informed Consent Forms and to the study by title and protocol number given on page one of the protocol. A copy of the signed and dated letter of approval will be provided to Auspex and designee prior to study commencement. Any written information and/or advertisements to be used for volunteer recruitment will be approved by the IEC/IRB prior to use.

9.1.2 Written Informed Consent

Informed consent will be obtained before the subject can participate in the study. If subject lacks the capacity to provide informed consent (as determined by an independent assessment by a qualified healthcare provider not directly involved in other study activities), a legally authorized representative must provide written informed consent and the subject must provide assent. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

It is the responsibility of the Site Investigator or designee to obtain written informed consent, using the most current informed consent form approved by the IRB/IEC and Sponsor, from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The Investigator or designee must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting written consent will be provided by the Investigator or designee.

For this study, each eligible subject will be required to provide written informed consent utilizing: Consent to participation in the study (Information Form/Informed Consent Form).

All eligible subjects and caregivers will have the study explained by the Site Investigator or designee. They will receive a full explanation, in lay terms, of the aims of the study, the discomfort, risks, and benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. It will be pointed out that they can withdraw from the study at any time without prejudice. Each subject will acknowledge receipt of this information by giving written informed consent for participation in the study. The subject and caregiver will be given a copy of the signed Information

Form/Informed Consent Form to retain.

9.1.3 *Emergency Contact with Investigator*

Suitable arrangements will be made for subjects to make contact with the Investigator or a medically qualified designee in the event of an emergency.

9.1.4 *Ethical Considerations*

This study will be carried out in accordance with the Principles of International Conference on Harmonization (ICH) Good Clinical Practice (GCP) which build upon the ethical codes contained in the Declaration of Helsinki.

The investigational site and the Sponsor agree to abide by the applicable guidelines for compensation for injury resulting from participating in a company-sponsored research project. Compensation will only be provided on the understanding that the provision of compensation does not amount to an admission of legal liability.

9.1.5 *Privacy Rule*

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number and/or randomization number will be recorded on the source documents and eCRF. If the subject name appears on any other document (e.g. pathologist report), it must be redacted before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the Sponsor, IEC/IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection laws. Laboratory specimens, including CAG testing, will be destroyed after testing is complete in accordance with each laboratory's standard procedures.

If the results of the study are published, the identity of all subjects will remain confidential.

The Investigator will maintain a list of the subject identification number to enable subjects' records to be identified.

9.2 *Protocol Amendments*

Any amendments to the protocol must be agreed upon by the Steering Committee and the Sponsor. Protocol amendments, if any, will be formalized and submitted to the IRB/IEC, per local rules, for written approval before implementation. The expedited review procedure for an amendment is appropriate only if subject safety is not an issue.

9.3 *Records Retention*

Following closure of the study, the Site Investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g. audit or inspection) and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff. The Sponsor will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard

applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or the Sponsor's standards/procedures; otherwise, the retention period will default to the time period specified in 21 CFR Part 312.57: Two years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

9.4 Study Monitoring

The Sponsor (or designee) is responsible for assuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded on the eCRFs. Subject confidentiality will be maintained.

In accordance with applicable regulations, GCP, and Sponsor (or designee) procedures, the CTCC will contact the site prior to the subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrolment rate. The visits will be conducted in accordance with the Sponsor's (or designee's) SOP and study monitoring plan.

In general, the Investigator agrees to fully cooperate with the monitor, allow the monitor direct access to all relevant documents, to allocate his/her time and the time of his/her staff to the monitor to discuss any findings and any relevant issues as needed.

9.4.1 Steering Committee

A Steering Committee (SC) has been established to provide overall supervision of the study and ensure that it is being conducted in accordance with the principles of Good Clinical Practice (GCP), Huntington Study Group constitutional bylaws, and the relevant regulations. The SC has reviewed the protocol, and will review and approve any protocol amendments, and provide advice to the investigators on the conduct of the trial. The SC members include representatives from Auspex, a biostatistician, the study PI and Co-PI, an experienced HD study coordinator, a psychiatrist and a HD patient advocate.

9.4.2 Clinical Monitoring

The Clinical Monitor for the study will review safety data on a monthly basis during study conduct, including aggregate laboratory and adverse event data, and laboratory alert values. The Clinical Monitor will review all Serious Adverse Events as they are reported. In addition, the Clinical Monitor will: Authorize enrollment based on review of eligibility information; approve enrollment of subjects with possible Gilbert's syndrome or two or more abnormal liver tests.

The investigative sites are to contact the Clinical Monitor to:

- Review drug suspensions and dose reductions, according to the procedures outlined in Section 5.2.5;
- Review all withdrawals from the study for medical reasons, as outlined in Section 6.14.

9.5 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor (or designee) may conduct a quality assurance audit. Regulatory agencies may also conduct a

regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection is requested, the Investigator and institution agree to immediately notify the Sponsor, to allow the auditor/inspector direct access to all relevant documents, and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

10 INFORMATION DISCLOSURE AND INVENTIONS

10.1 Ownership

All information provided by Auspex, and all data and information generated by a study site and/or by Auspex's contractors and subcontractors as part of the study (other than a study subject's medical records), are the sole property of Auspex.

All rights, title and interests in any inventions, discoveries, know-how and other intellectual or industrial property rights which are conceived or reduced to practice during the course of or as a result of the study are the sole property of Auspex and are hereby assigned to Auspex.

If any written contract is executed between Auspex and the study site for the conduct of the study, or between Auspex and a contractor for support of the study, and such contract includes ownership provisions that are inconsistent with or otherwise differ from the foregoing sentence, then with respect to such inconsistency or difference, that contract's ownership provisions regarding inventions and other intellectual or industrial property rights shall control.

10.2 Confidentiality

All information provided by Auspex and all data and information generated by the site as part of the study, (other than a subject's medical records), will be kept confidential by the Investigator and other site staff. The Investigator or other site personnel will not use this information and data for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the Investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

10.3 Publication

Auspex recognizes the importance of communicating medical study data and therefore encourages publication in peer-reviewed scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts and presentations based on the data from this trial are described in the Clinical Trial Agreement.

11 REFERENCES

1. Baillie TA. The use of stable isotopes in pharmacological research. *Pharmacol Rev.* 1981;33(2):81-132.
2. Guyton AC. *Textbook of Medical Physiology*, 8th Ed. Philadelphia, PA: W.B. Saunders; 1991. p. 274.
3. Chang R. *Chemistry*, 9th Ed.: McGraw-Hill; 2007.
4. Kushner DJ, Baker A, Dunstall TG. Pharmacological uses and perspectives of heavy water and deuterated compounds. *Can J Physiol Pharmacol.* 1999;77(2):79-88.
5. Di Costanzo L, Moulin M, Haertlein M, Meilleur F, Christianson DW. Expression, purification, assay, and crystal structure of perdeuterated human arginase I. *Arch Biochem Biophys.* 2007;465(1):82-9.
6. Fisher SJ, Helliwell JR. An investigation into structural changes due to deuteration. *Acta Crystallogr A.* 2008;64(Pt 3):359-67.
7. Blagojevic N, Storr G, Allen JB. Role of heavy water in boron neutron capture therapy. In: Zamenhof R, Solares G, Harling O, editors. *Dosimetry and treatment planning for neutron capture therapy.* Madison, WI1994.
8. Collins ML, Eng S, Hoh R, Hellerstein MK. Measurement of mitochondrial DNA synthesis in vivo using a stable isotope-mass spectrometric technique. *J Appl Physiol.* 2003;94(6):2203-11.
9. Kassis AN, Jones PJ. Changes in cholesterol kinetics following sugar cane policosanol supplementation: a randomized control trial. *Lipids Health Dis.* 2008;7(1):17.
10. Leitch CA, Jones PJ. Measurement of human lipogenesis using deuterium incorporation. *J Lipid Res.* 1993;34(1):157-63.
11. Neese RA, Misell LM, Turner S, Chu A, Kim J, Cesar D, et al. Measurement in vivo of proliferation rates of slow turnover cells by 2H₂O labeling of the deoxyribose moiety of DNA. *Proc Natl Acad Sci U S A.* 2002;99(24):15345-50.
12. Strawford A, Antelo F, Christiansen M, Hellerstein MK. Adipose tissue triglyceride turnover, de novo lipogenesis, and cell proliferation in humans measured with 2H₂O. *Am J Physiol Endocrinol Metab.* 2004;286(4):E577-88.
13. Hellerstein MK, Hoh RA, Hanley MB, Cesar D, Lee D, Neese RA, et al. Subpopulations of long-lived and short-lived T cells in advanced HIV-1 infection. *The Journal of clinical investigation.* 2003;112(6):956-66.
14. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica.* 1983;67(6):361-70.
15. The Columbia Suicide Severity Rating Scale [cited 2012 May 18]. Available from: http://www.cssrs.columbia.edu/about_cssrs.html.
16. Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials, DRAFT GUIDANCE. September 2010.
17. Huntington-Study-Group. Unified Huntington disease rating scale: reliability and consistency. *Mov Disord.* 1996;11:136-42.

18. Barnes TR. A rating scale for drug-induced akathisia. *The British journal of psychiatry : the journal of mental science.* 1989;154:672-6.
19. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14(6):540-5.
20. Manor Y, Giladi N, Cohen A, Fliss DM, Cohen JT. Validation of a swallowing disturbance questionnaire for detecting dysphagia in patients with Parkinson's disease. *Mov Disord.* 2007;22(13):1917-21.
21. Cohen JT, Manor Y. Swallowing disturbance questionnaire for detecting dysphagia. *The Laryngoscope.* 2011;121(7):1383-7.
22. Stocking CB, Hougham GW, Danner DD, Patterson MB, Whitehouse PJ, Sachs GA. Speaking of research advance directives: planning for future research participation. *Neurology.* 2006;66(9):1361-6.
23. Commission NBA. Research involving persons with mental disorders that may affect decision-making capacity. Vol. 2. Commissioned Papers. Rockville, MD: US Government Printing Office; 1999.

12 APPENDICES

Appendix 1: Site Investigator Signature Page

- I agree to implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- I have read and agree to comply with the Investigator obligations stated in this protocol. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of subjects.
- I agree to conduct in person or to supervise the trial.
- I agree to ensure that all that assist me in the conduct of the study are aware of their obligations.
- I agree to maintain all information supplied by Auspex Pharmaceuticals, Inc. in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Principal Investigator:

Print Name

Signature

Date

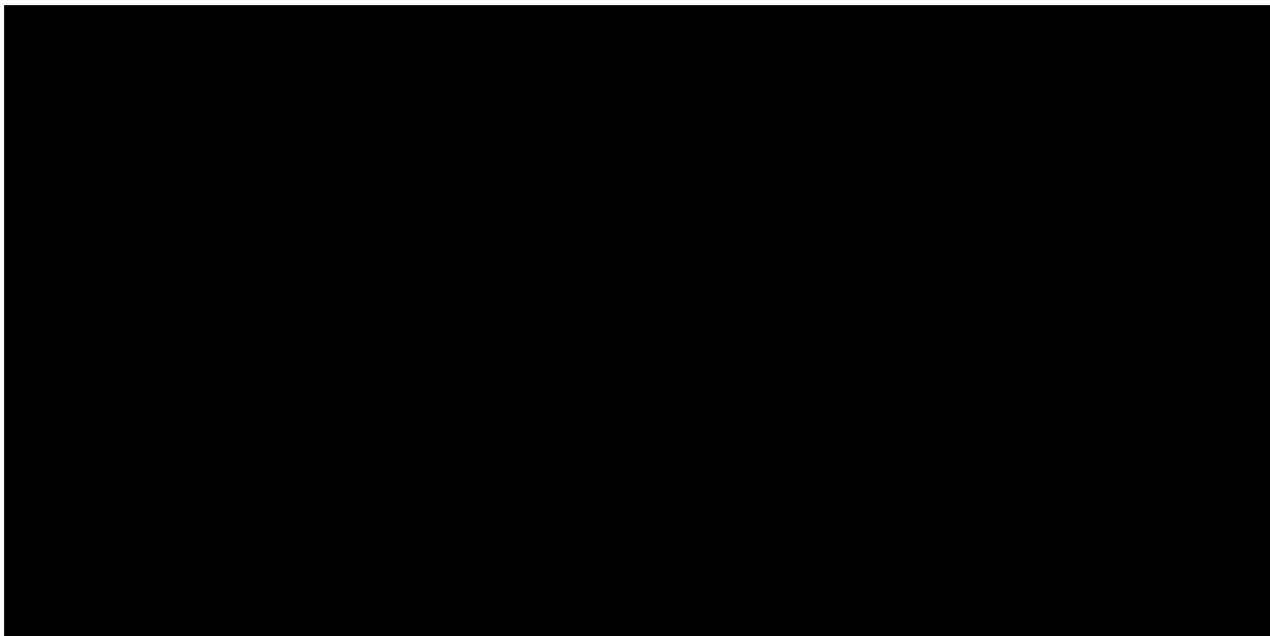
Appendix 2: Unified Huntington's Disease Rating Scale (UHDRS)

Appendix 3: Hospital Anxiety and Depression Scale (HADS)

Appendix 4: Columbia Suicidality Severity Rating Scale (C-SSRS) – Baseline

Appendix 5: Columbia Suicidality Severity Rating Scale (C-SSRS) – Since Last Visit

Appendix 6: Unified Parkinson's Disease Rating Scale (UPDRS): Speech



Fahn S, Elton RL, Members of the UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent developments in Parkinson's disease, vol 2. Florham Park, NJ: Macmillan Health Care Information, 1987:153-163, 293-304

Appendix 7: Montreal Cognitive Assessment (MoCA[®])

Appendix 8: Epworth Sleepiness Scale (ESS)

Appendix 9: Barnes Akathisia Rating Scale (BARS)



Citation: Barnes TR: A Rating Scale for Drug-Induced Akathisia. *British Journal of Psychiatry* 154:672-676, 1989.

Appendix 10: Swallowing Disturbance Questionnaire (SDQ)

Appendix 11: Strong CYP2D6 Inhibitors

Subject's receiving any of these strong CYP2D6 inhibitors will have a maximal dose of SD-809 ER of 42 mg per day.

- Bupropion
- Fluoxetine
- Paroxetine

Appendix 12: Prohibited or restricted QT Prolonging Drugs

Generic	Brand Name	Class/Clinical Use	Note
Amiodarone	Cordarone [®] , Pacerone [®]	Anti-arrhythmic / abnormal heart rhythm	
Arsenic trioxide	Trisenox [®]	Anti-cancer / Leukemia	
Azithromycin	Zithromax [®]	Antibiotic / bacterial infection	
Bepridil	Vascor [®]	Anti-anginal / heart pain	
Chloroquine	Aralen [®]	Anti-malarial / malaria infection	
Chlorpromazine	Thorazine [®]	Anti-psychotic/ Anti-emetic / schizophrenia	
Citalopram	Celexa [®]	Anti-depressant / depression	See Appendix 16 for dosing information
Clarithromycin	Biaxin [®]	Antibiotic / bacterial infection	
Disopyramide	Norpace [®]	Anti-arrhythmic / abnormal heart rhythm	
Dofetilide	Tikosyn [®]	Anti-arrhythmic / abnormal heart rhythm	
Domperidone	Motilium [®]	Anti-nausea / nausea	Not available in U.S.
Droperidol	Inapsine [®]	Sedative; Anti-nausea/anesthesia adjunct, nausea	
Erythromycin	E.E.S. [®] , Erythrocin [®]	Antibiotic; GI stimulant; GI motility	
Escitalopram	Lexapro [®] , Cipralex [®]	Anti-depressant / Anxiety disorders	See Appendix 16 for dosing information
Flecainide	Tambocor [®]	Anti-arrhythmic / abnormal heart rhythm	
Halofantrine	Halfan [®]	Anti-malarial / malaria infection	
Haloperidol	Haldol [®]	Anti-psychotic / schizophrenia, agitation	
Ibutilide	Corvert [®]	Anti-arrhythmic / abnormal heart rhythm	
Levomethadyl	Orlaam [®]	Opiate agonist/pain control, narcotic dependence	Not available in U.S.
Mesoridazine	Serentil [®]	Anti-psychotic / schizophrenia	
Methadone	Dolophine [®]	Opiate agonist/pain control, narcotic dependence	
Methadone	Methadose [®]	Opiate agonist/pain control, narcotic dependence	
Moxifloxacin	Avelox [®]	Antibiotic / bacterial infection	
Pentamidine	NebuPent [®] , Pentam [®]	Anti-infective / pneumocystis pneumonia	
Pimozide	Orap [®]	Anti-psychotic / Tourette's tics	
Probucol	Lorelco [®]	Antilipemic / Hypercholesterolemia	Not available in U.S.
Procainamide	Pronestyl [®] , Procan [®]	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Quinaglute, Cardioquin	Anti-arrhythmic / abnormal heart rhythm	
Quetiapine	Seroquel [®] , Seroquel XR [®]	Anti-psychotic / schizophrenia	
Sevoflurane	Ulane [®] , Sojour [®]	Anesthetic, general / anesthesia	
Sotalol	Betapace [®]	Anti-arrhythmic / abnormal heart rhythm	
Sparfloxacin	Zagam [®]	Antibiotic / bacterial infection	Not available in U.S.
Thioridazine	Mellaril [®]	Anti-psychotic / schizophrenia	

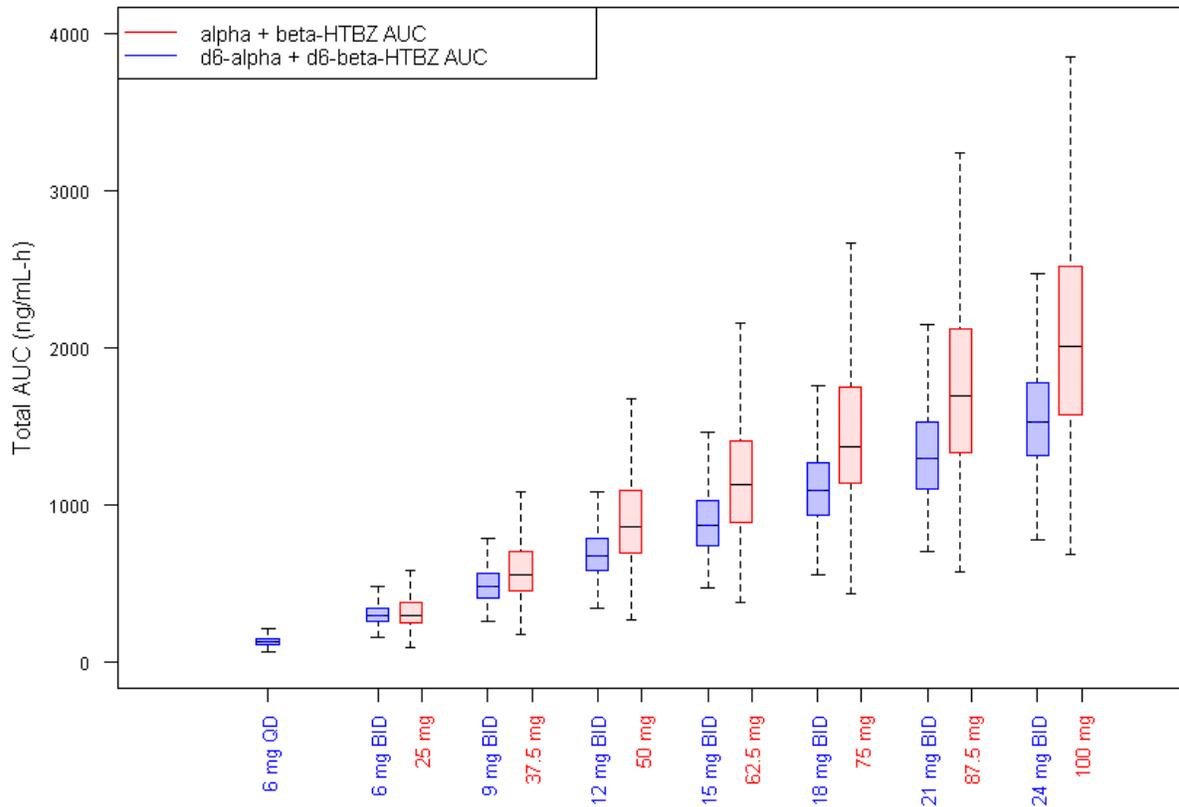
Vandetanib	Caprelsa®	Anti-cancer / Thyroid cancer	
Vardenafil	Levitra®	Phosphodiesterase inhibitor / vasodilator	

Appendix 13: Prohibited Antipsychotic Drugs

Typical/First Generation Antipsychotics	Atypical/Second Generation Antipsychotics
Chlorpromazine (Thorazine, Largactil)	Aripiprazole (Abilify)
Fluphenazine (Prolixin)	Asenapine Maleate (Saphris)
Haloperidol (Haldol, Serenace)	Clozapine (Clozaril)
Loxapine (Loxapac, Loxitane)	Iloperidone (Fanapt)
Molindone (Moban)	Lurasidone (Latuda)
Perphenazine (Trilafon)	Olanzapine (Zyprexa)
Pimozide (Orap)	Olanzapine/Fluoxetine (Symbyax)
Prochlorperazine (Compazine)	Paliperidone (Invega)
Thioridazine (Mellaril)	Quetiapine (Seroquel)
Thiothixene (Navane)	Risperidone (Risperdal)
Trifluoperazine (Stelazine)	Ziprasidone (Geodon)
Promethazine (Phenergan) containing compounds	

Appendix 14: Simulated Exposures of Total ($\alpha+\beta$)-HTBZ for Tetrabenazine and SD-809

Comparison of Simulated Exposures (AUC_{0-24}) of Total ($\alpha+\beta$)-HTBZ for Tetrabenazine (pink) and SD-809 ER (blue) at Steady State for Various Dose Regimens in CYP2D6 Extensive/Intermediate Metabolizers



Note: Box plots represent 25/50(median)/75th percentiles and whiskers represent 95% CI

Dose information on x-axis: SD-809 ER (blue text) is dose regimen and TBZ (red text) is total daily dose

Appendix 15: Simulated Exposures (AUC₂₄) of Total (α + β)-HTBZ for Initial SD-809 Regimens at Steady State in CYP2D6 Poor Metabolizers

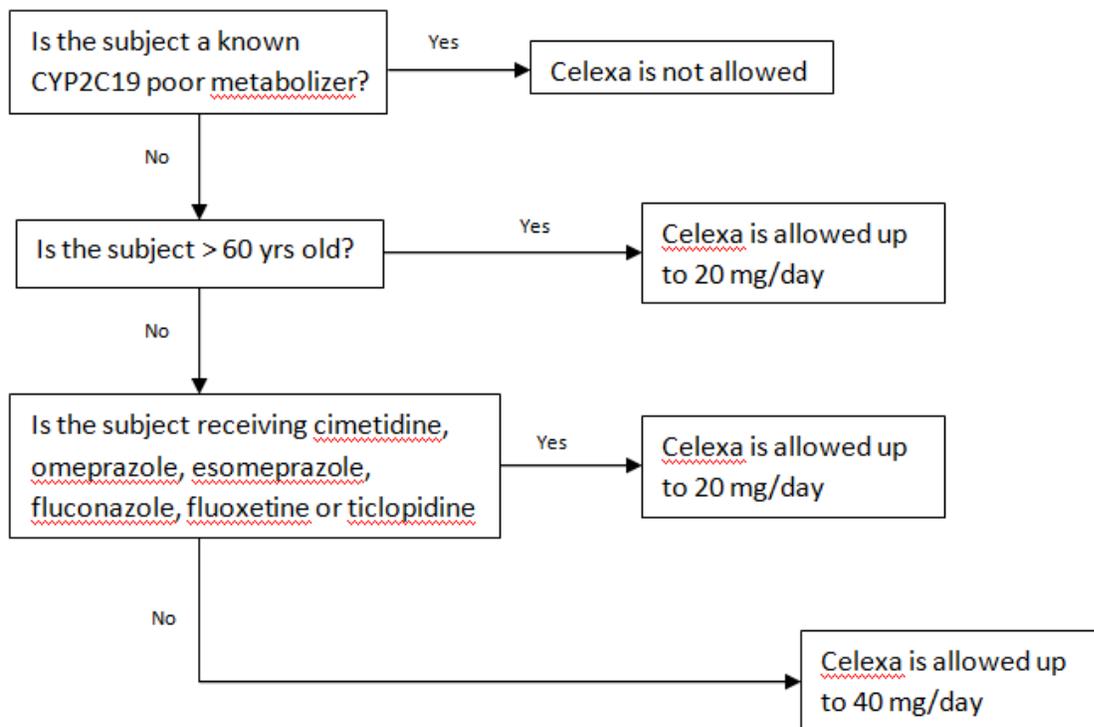
Scenarios	Treatment	Total daily dose	Regimens	AUC _{24ss} (h•ng/mL)
1	TBZ	25 mg	12.5 mg BID	1510 [819-2943]
	SD-809	12 mg	6 mg BID	1061 [635-2034]
2	TBZ	37.5 mg	12.5 mg TID 25/12.5 12.5/25	2750 [1499-5326] 2768 [1563-5250]
	SD-809	18 mg	12/6 mg	1740 [1058-3105]
3	TBZ	50 mg	25 mg BID 25/12.5/12.5 12.5/25/12.5 12.5/12.5/25	4200 [2296-8155] 4228 [2394-8030]
	SD-809	24 mg	12 mg BID	2435 [1451-4723]

Appendix 16: Celexa and Lexapro (Cipralext) Dosing Information

Citalopram (Celexa) is allowed with the following restrictions:

- a) If the subject is a known CYP2C19 poor metabolizer, Celexa is not allowed.
- b) If the subject is > 60 years old **or** is receiving cimetidine, omeprazole, esomeprazole, fluconazole, fluoxetine or ticlopidine, the maximum allowed dose is 20 mg/day.
- c) If the subject is ≤ 60 years old and is not receiving any of the medications in (b) above, the maximum allowed dose is 40 mg.

The following flowchart may be used to determine the maximum allowable dose of Celexa:



Escitalopram (Lexapro or Cipralext) is allowed with the following restrictions:

Age	Maximum daily dose
< 65 years	20 mg
≥ 65 years	10 mg