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PROTOCOL NUMBER: 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**

First Time Use of SD-809 ER in HD (First-HD)

February 27, 2014

Amendment 3

Development Phase: 3

STUDY CONTACTS

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PROTOCOL SYNOPSIS

PROTOCOL	SD-809-C-15
TITLE	A Randomized, Double Blind, Placebo Controlled Study of SD-809 Extended Release for the Treatment of Chorea associated with Huntington Disease
Running Title	First Time Use of SD-809 ER in HD (First-HD)
PHASE	3
INDICATION	Treatment of chorea associated with Huntington disease (HD)
NO. SITES	Approximately 30
OBJECTIVES	<ul style="list-style-type: none"> • To evaluate the efficacy of SD-809 extended release (ER) to reduce the chorea associated with HD • To evaluate the safety and tolerability of titration and maintenance therapy with SD-809 ER
STUDY POPULATION	Male and female adult subjects with manifest HD and chorea
STUDY DESIGN	<p>This is a randomized, double blind, placebo controlled parallel group study in which subjects with chorea associated with HD will be invited to participate. Subjects will undergo an independent evaluation by a qualified healthcare provider to determine their capacity to provide informed consent. Subjects who qualify for the study will be randomized to receive either SD-809 ER or placebo in a 1:1 (SD-809 ER to placebo) ratio and the randomization will be stratified by prior exposure to tetrabenazine (previously exposed versus not previously exposed to tetrabenazine). Subjects will be titrated to an optimal dose level of study drug, followed by maintenance therapy at that dose. The overall treatment period will be 12 weeks in duration. The titration period will last 8 weeks, the maintenance period will be 4 weeks, followed by a washout period of 1 week. To provide a systematic examination for independent rating of chorea, a limited motor examination will be video recorded using a standard protocol at Screening, Baseline and at Weeks 9 and 12.</p> <p>Screening period (up to 4 weeks): Subjects will undergo an independent evaluation by a qualified healthcare provider to determine their capacity to provide informed consent. After informed consent is obtained, subjects who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history, physical and neurological examination, laboratory testing, 12-lead ECG, and scales to evaluate HD. Subjects will return to the clinic for a Baseline evaluation on Day 0 to re-confirm eligibility. Subjects who remain eligible for participation in the study will be randomized at the Baseline visit and will initiate therapy with either SD-809 ER or placebo on the day after the Baseline visit (Day 1). For all visits in the screening period, subjects will be required to be accompanied by a caregiver. If the capacity assessment deems the subject not able to sign consent, the legally authorized representative will also need to accompany the subject at the visit requiring signing of consent and subject assent.</p> <p>Titration period (8 weeks): All subjects and caregivers will interact weekly with the clinical site, either by telephone contact or clinic visit, through Week 8 of the titration period, in order to evaluate safety and establish a dose of study drug that adequately controls chorea and is well-tolerated. Safety evaluations during titration include Unified Huntington Disease Rating Scale (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[®], Ciprallex[®]) will have additional ECGs during the titration period as specified in the Schedule of Events.</p>
STUDY DESIGN (Continued)	

	<p>In person study visits will be scheduled at Weeks 2, 4, and 6 after initiating therapy and telephone contacts will be scheduled for Weeks 1, 3, 5, 7 and 8 after initiating therapy. 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 increased on a weekly basis 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. Although dose adjustments may be made up to and including Week 7, if a subject reaches a stable dose before Week 7, the subject will continue on that dose for the duration of the titration period and through the maintenance period. Once adequate control of chorea has been achieved, the dose of study drug should not be increased further. If a subject experiences a “clinically significant” 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 and caregiver’s reports of adverse events and chorea control, the clinical assessment of safety and efficacy by the investigator, as well as information from rating scales including the Unified Huntington Disease Rating Scale (UHDRS), the Hospital Anxiety and Depression Scale (HADS), the Swallowing Disturbance Questionnaire (SDQ), the Unified Parkinson’s Disease Rating Scale (dysarthria item) (UPDRS [dysarthria]), the Barnes Akathisia Rating Scale (BARS), the Epworth Sleepiness Scale (ESS), and the Columbia Suicide Severity Rating Scale (C-SSRS). At the end of the titration period, the subject’s dose will be established for the maintenance period.</p> <p>Maintenance period (4 weeks): Subjects will continue to receive their maintenance dose over the next 4 weeks (dose reductions for adverse events are allowed) and will return for in person visits at Weeks 9 and 12 for evaluation of safety, efficacy and pharmacokinetics (PK). In addition, there will be a telephone contact at Week 10 to evaluate safety. At the end of the maintenance period (Week 12), subjects will undergo a complete evaluation, including physical and neurological exam, safety labs and 12-lead ECG and performance of all rating scales. If a subject requires a dose reduction during the maintenance period based on a telephone contact, an unscheduled clinic visit should be conducted.</p> <p>Washout (1 week): All subjects will discontinue study drug after the Week 12 visit and will return one week later for evaluation of safety, chorea and motor function. Subjects who complete the study and were tolerating study drug may be eligible to participate in a long term safety study of SD-809 ER. Subjects <u>not</u> participating in the long term safety study of SD-809 ER will have a follow up telephone contact four weeks after their last dose of study drug.</p>
<p>FORMULATION</p>	<ul style="list-style-type: none"> • SD-809 extended release (ER) tablets are available in three dose strengths: 6, 9 and 12 mg, all of which are identical in size, shape and color (white). • Placebo tablets are identical in appearance to SD-809 ER.

¹ See [Section 7](#) for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

DOSE REGIMEN	<p>Study drug will be dosed as follows:</p> <ul style="list-style-type: none"> • All treatment regimens will be administered twice daily with meals, approximately 10 hours apart during the day. • The starting dose will be SD-809 ER 6 mg or placebo in the AM; both treatment arms will receive placebo in the PM • The dose of study drug may be adjusted weekly in increments of 6mg/day (SD-809 ER or placebo) during the titration period to identify a dose level that reduces chorea and is well-tolerated. <ul style="list-style-type: none"> • Dose reductions are in increments of 6 mg per day • The maximum total daily dose of SD-809 ER is 48 mg (24 mg BID), unless the subject is receiving a potent CYP2D6 inhibitor (See Appendix 16), in which case the maximum total daily dose is 36 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
SAMPLE SIZE	<p>Approximately 90 subjects (approx. 45 subjects in the SD-809 ER arm and approx. 45 subjects in the placebo arm) will be enrolled.</p>
INCLUSION CRITERIA	<ol style="list-style-type: none"> 1. Subject is at least 18 years of age or the age of majority (whichever is older) at Screening. 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 has a Total Maximal Chorea Score (TMC) ≥ 8 at Screening and Baseline. (<u>Note</u>: The Baseline TMC may be < 8 if the average of the Screening and Baseline scores is ≥ 8 and the difference between the Screening and Baseline scores is no more than 4). 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 <u>or</u>, 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. Female subjects of childbearing potential² 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

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 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 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.

	<p>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 enrollment. • Stable hormonal contraception (with approved oral, transdermal, or depot regimen) for at least 3 months prior to screening. <p>8. 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>
<p>INCLUSION CRITERIA (Continued)</p>	<ul style="list-style-type: none"> • 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 Screening, Baseline and Weeks 4, 9 and 12 Visits. Caregivers will be encouraged to attend other visits. <p>9. Subject is able to ambulate without assistance for at least 20 yards (Note: The use of assistive devices (i.e., walker, cane) is permitted during ambulation).</p>
<p>EXCLUSION CRITERIA</p>	<ol style="list-style-type: none"> 1. Subject has a serious untreated or undertreated psychiatric illness, such as depression, at Screening or Baseline. <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 17 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: <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 4. Subject has a score ≥ 11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) at Screening or Baseline. 5. Subject has an unstable or serious medical or psychiatric illness at Screening or Baseline. 6. Subject has received tetrabenazine within 6 months prior to Screening. 7. Subject has received any of the following concomitant medications within 30 days of Screening or Baseline: <ul style="list-style-type: none"> • Antipsychotics (See Appendix 18) • Metoclopramide • Monoamine oxidase inhibitors (MAOI) • Levodopa or dopamine agonists • Reserpine • Amantadine • Memantine 8. Subject has a score of ≥ 11 on the Swallowing Disturbance Questionnaire (SDQ) at Screening. 9. Subject has a Unified Parkinson's Disease Rating Scale (UPDRS) dysarthria score

	of ≥ 3 at Screening.
EXCLUSION CRITERIA (Continued)	<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 19 for Celexa and Lexapro (CipraleX) dosing information • See Appendix 17 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 medical 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> <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 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.</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>
SAFETY PARAMETERS	Safety and tolerability will be assessed throughout the study by monitoring the following parameters:

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 18](#)):

- 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>SAFETY PARAMETERS (Continued)</p>	<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 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[®])
<p>EFFICACY ENDPOINTS</p>	<p><u>Primary Endpoint:</u> The change in Total Maximal Chorea Score (TMC) from Baseline (defined for each subject as the average of values from the Screening and Day 0 visits) to maintenance therapy (defined for each subject as the average of values from the Week 9 and Week 12 visits).</p> <p><u>Key Secondary Endpoints:</u></p> <ul style="list-style-type: none"> • The proportion of subjects who are a treatment success at the end of the end of therapy, based on the Patient Global Impression of Change (PGIC). A treatment success is defined as Much or Very Much Improved on the PGIC at the Week 12 visit. The PGIC is a 7-point Likert Scale, ranging from very much worse to very much improved (Appendix 11). • The proportion of subjects who are a treatment success at the end of the end of therapy, based on the Clinical Global Impression of Change (CGIC). A treatment success is defined as Much or Very Much Improved on the CGIC the Week 12 visit. • Change in the Short Form 36 Health Survey (SF-36) Physical component summary score from Baseline to Week 12. • Change in the Berg Balance Test (BBT) score from Baseline to Week 12 	
<p>SAFETY ENDPOINTS</p>	<ul style="list-style-type: none"> • Incidence of adverse events (AEs), serious AEs (SAEs), severe AEs, drug related AEs, AEs leading to withdrawal, AEs during titration and AEs during maintenance therapy • Observed values and changes in clinical laboratory parameters (hematology, chemistry, and urinalysis) • Observed values and changes 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, SDQ, UPDRS (dysarthria), BARS, HADS, ESS, C-SSRS, and MoCA[®] 	
<p>PHARMACOKINETICS</p>	<p>Blood samples will be obtained for measurement of plasma concentrations of SD-809, alpha-dihydropyridazinone (α-HTBZ), beta-(β)-HTBZ, total (α+β)-HTBZ and other metabolites, as required. At the Week 9 and Week 12 Visits, subjects will have blood sampling for PK as follows:</p> <ul style="list-style-type: none"> • Week 9: <ul style="list-style-type: none"> ○ Sample 1 upon arrival at clinic and ○ Sample 2 at least 2 hours after sample 1 • Week 12: <ul style="list-style-type: none"> ○ Sample 1 upon arrival in clinic and ○ Sample 2 at least 3 hours after sample 1 • <u>Note:</u> The time between samples should be maximized in order to provide the most useful information. <p>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 degrees C or below.</p>	

<p>PHARMACO-KINETICS (Continued)</p>	<p>Subjects will be provided with a diary to record meal and dosing times on PK sampling days during maintenance only. Prior to clinic visits on Weeks 9 and 12 (Visits 6 and 7), 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. Subjects should take their usual morning dose of study drug at home and have initial blood sampling for PK upon arrival in the clinic on these visits.</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 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>
<p>STATISTICS</p>	<p><u>Efficacy:</u> The primary efficacy endpoint for this study is the change in Total Maximal Chorea Score (TMC) from Baseline (defined for each subject as the average of values from the Screening and Day 0 visits) to maintenance therapy (defined for each subject as the average of values from the Week 9 and Week 12 visits). The primary analysis will be carried out using an analysis of covariance (ANCOVA) model with the change from baseline in TMC as the dependent variable, treatment group and the randomization stratification variable as factors, and the baseline TMC score as a covariate. The SD-809 ER and placebo groups will be compared using a two-sided test at the 5% level of significance.</p> <p><u>Sample Size:</u> Given a 1:1 randomization ratio (SD-809 ER to placebo), and assuming that the standard deviation of the TMC change from Baseline to Week 12 is equal to 3.7, a sample size of 80 subjects will provide 90% power to detect a treatment difference of 2.7 units change in the total maximal chorea score. Accounting for a dropout rate of 10%, approximately 90 subjects will be enrolled.</p> <p>The key secondary endpoints will be analyzed using a hierarchical (gatekeeping) test procedure. If the primary analysis is statistically significant ($p < 0.05$), then the first key secondary endpoint will be analyzed, also at the 5% level of significance. If the first key secondary endpoint is statistically significant, then the second key secondary endpoint will be similarly analyzed, etc. For any analysis that is not statistically significant, all subsequent analyses of key secondary endpoints will be exploratory rather than confirmatory.</p> <p><u>Safety:</u> Safety data will be summarized descriptively for each treatment group. 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 treatment group. 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>Demographic information will be presented for each subject and summarized by treatment group. Treatment-emergent adverse events and laboratory, vital sign, and ECG parameters will be summarized by treatment group. 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 by treatment group.</p> <p><u>Pharmacokinetics:</u> A population pharmacokinetic analysis will be performed using data from all subjects to examine the pharmacokinetics of SD-809 and to explore the potential effect of various covariates on the pharmacokinetics of SD-809 and, if possible, explore the relationship between pharmacokinetics and change in TMC. The population pharmacokinetic analysis will be discussed in detail in a prospective Statistical Analysis Plan.</p>

SCHEDULE OF EVENTS

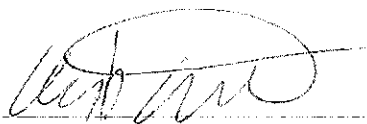
Week	Screening		Titration								Maintenance			Follow Up		Uns	
	Up to -4	BL ¹	1	2	3	4	5	6	7	8	9	10	12/ ET ²	13	16 ³		
Visit Windows (in days)		0	± 1		± 3										n/a		
Activity	Visit	V1	V2	T1	V3	T2	V4	T3	V5	T4	T5	V6	T6	V7	V8	T7	U
Clinic Visit	X	X		X		X		X				X		X	X		X
Telephone Contact			X		X		X		X	X		X			X		
Evaluate/Adjust Dose of study medication			X	X	X	X	X	X	X								
Evaluate Capacity for informed consent ⁴	X																
Informed Consent/Assent ⁴	X																
Selection Criteria	X	X ⁵															
Medical History/Demographics	X																
Vital Signs/Weight	X	X ⁶		X		X ⁶		X				X		X ⁶	X		X
Physical Examination	X ⁷	X												X			X ^{7,8}
Complete Neurological Exam	X													X			X ⁸
Height	X																
12-lead ECG	X			X ⁹		X ⁹		X ⁹				X ⁹		X			X ⁸
Chemistry/Hematology/UA	X ¹⁰	X				X								X			X ⁸
CAG Repeat	X																
Randomization via IWRS ¹¹		X															
Blinded CYP2D6 Genotype		X															
Pregnancy Test/FSH ¹²	S	U															
Virology Screen (HBsAg)	X																
Blood Sampling for Pharmacokinetics												X ¹³		X ¹³			X ¹⁸
HADS	X	X		X		X		X				X		X	X		X
C-SSRS ¹⁴	X	X		X		X		X				X		X	X		X
MoCA [®]		X				X						X		X			
Video recording of Chorea ¹⁵	X	X										X		X			
UHDRS - Motor	X	X		X		X		X				X		X	X		X
UHDRS - Cognition		X				X						X		X			
UHDRS - Behavior		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		X
Berg Balance Test (BBT)		X		X		X		X				X		X	X		X
Swallowing Disturbance Questionnaire (SDQ)	X	X		X		X		X				X		X	X		X
Barnes Akathisia Rating Scale (BARS)		X		X		X		X				X		X	X		X
Epworth Sleepiness Scale (ESS)		X		X		X		X				X		X	X		X
Patient Global Impression of Change						X						X		X			
Clinical Global Impression of Change						X						X		X			
SF-36		X												X			
Dispense Study Drug via IWRS		X ¹⁶	X	X ¹⁷	X	X ¹⁷	X	X ¹⁷	X	X	X	X					
Assess Drug Accountability/Compliance				X		X		X				X		X			
Assess Adverse Events		X	X	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	X	X

- 1 BL: Baseline visit (Day 0) will occur on the day before the scheduled first dose of SD-809 ER (Day 1)
 - 2 ET: Early termination visit
 - 3 Subjects not participating in the long term safety study will have a follow up safety telephone contact 4 weeks after the Week 12 visit.
 - 4 Capacity assessment and informed consent may be performed >4 weeks prior to first dose, as necessary to allow for washout from prohibited medications.
 - 5 Selection criteria to be re-evaluated at Baseline include Inclusion criterion 3 and Exclusion criteria 1-7 and 16.
 - 6 Perform orthostatic blood pressure and pulse after subject is in standing position for at least 3 minutes.
 - 7 Brief physical examination includes evaluation of the cardiovascular, respiratory, and abdominal systems/regions.
 - 8 Assessment to be completed at Investigator's discretion
 - 9 For subjects on allowed doses of Celexa or Lexapro (Ciprallex):
 - Week 2: A 12-lead ECG is required at this visit.
 - Weeks 4, 6, 9: If the dose of study drug has been increased since the last ECG, a 12-lead ECG is required at this visit.
 - 10 Screening labs to include Prothrombin Time (PT)
 - 11 Eligibility data to be reviewed by medical monitor prior to randomization via IWRS.
 - 12 Serum follicle stimulating hormone (FSH) level to be assessed in post-menopausal subjects
 - 13 Remind subjects 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. Subjects will take their usual morning dose of study drug at home and have blood sampling for PK upon arrival in the clinic on these visits. Subjects will have a second PK sample drawn at least 2 hours (Week 9) or 3 hours (Week 12) after their initial sample (Ideally, this interval should be as long as possible to obtain the most useful information). 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.
 - 14 At Screening, administer the C-SSRS Baseline version (see [Appendix 4](#)). At Baseline and every visit thereafter, administer the C-SSRS Since Last Visit version (see [Appendix 5](#)).
 - 15 Chorea will be videotaped using a standardized protocol. See [Section 6.8.6](#) and [Appendix 15](#).
 - 16 Initial drug supply will be provided in clinic at the Baseline visit.
 - 17 If visit occurs such that re-dispensing of study drug cannot occur in time to be received by the following day, study drug remaining from the prior week should be re-dispensed if the patient is not undergoing a dose reduction. Instruct the subject to take study drug from the prior week's package until the new package of study drug is received.
 - 18 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.
- [Uns] Unscheduled Visit
[V#] Clinic visit number
[T#] Telephone visit number
[S] Serum pregnancy test for women of childbearing potential only
[U] Urine pregnancy test for women of childbearing potential only

PROTOCOL SIGNATURE PAGE

**A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED STUDY OF
SD-809 EXTENDED RELEASE FOR THE TREATMENT OF CHOREA
ASSOCIATED WITH HUNTINGTON DISEASE (FIRST-HD)**

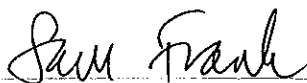
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TABLE OF CONTENTS

STUDY CONTACTS	2
PROTOCOL SYNOPSIS	3
SCHEDULE OF EVENTS	10
PROTOCOL SIGNATURE PAGE	12
TABLE OF CONTENTS	13
LIST OF APPENDICES	17
LIST OF ABBREVIATIONS	18
1 INTRODUCTION	21
1.1 Disease Background	21
1.2 Tetrabenazine	21
1.3 Deuterium	22
1.3.1 Clinical Experience with Deuterium	22
1.4 SD-809 (d ₆ -Tetrabenazine)	23
2 STUDY OBJECTIVES	24
3 INVESTIGATIONAL PLAN	24
3.1 Study Design	24
3.2 Rationale for Study Design	26
3.3 Rationale for Dose Selection	26
4 STUDY POPULATION	26
4.1 Population Characteristics	26
4.2 Inclusion Criteria	27
4.3 Exclusion Criteria	28
5 STUDY TREATMENT	30
5.1 Investigational Product	30
5.2 Blinding	30
5.3 Randomization to Study Drug	30
5.4 Unblinding During the Study	30
5.5 Treatment Regimen	31
5.6 Titrating Study Medication	32
5.6.1 Dose Reduction or Suspension	33
5.7 Treatment Administration	33
5.8 Accountability of Study Drug	33

5.9	Study Drug Compliance	34
6	STUDY METHODS AND PROCEDURES	34
6.1	Screening Period	34
6.1.1	Screening Visit (up to Week -4)	34
6.1.2	Baseline Visit (Day 0).....	36
6.2	Titration Period	37
6.2.1	Telephone Contacts (Week 1 [± 1 day] and 3, 5, and 7 [all ± 3 days])	38
6.2.2	Clinic Visits (Weeks 2, 4, and 6 [all ± 3 days]).....	38
6.2.3	Telephone Contact (Week 8 ± 3 days).....	39
6.3	Maintenance Period.....	39
6.3.1	Clinic Visit (Week 9 ± 3 days)	39
6.3.2	Telephone Contact (Week 10 ± 3 days).....	40
6.3.3	Clinic Visit (Week 12 ± 3 days or Early Termination).....	41
6.4	Post-Treatment Safety Follow Up.....	42
6.4.1	Clinic Visit (Week 13 ± 3 days)	42
6.4.2	Telephone Contact (Week 16 ± 3 days).....	42
6.5	Unscheduled Visit(s).....	43
6.6	Safety Evaluations.....	43
6.6.1	Demographics and Medical History	43
6.6.2	Physical Examination.....	43
6.6.3	Complete Neurological Examination.....	44
6.6.4	Vital Signs.....	44
6.6.5	Orthostatic Blood Pressure and Pulse.....	44
6.6.6	Laboratory Tests	45
6.6.7	12-lead Electrocardiogram (ECG)	45
6.6.8	Detecting Adverse Events.....	45
6.7	Rating Scales	46
	Subject completed assessments will be available in English, Spanish and French.....	46
6.7.1	Hospital Anxiety and Depression Scale (HADS).....	46
6.7.2	Columbia Suicide Severity Rating Scale (C-SSRS).....	46
6.7.3	Unified Huntington Disease Rating Scale (UHDRS).....	46
6.7.4	Montreal Cognitive Assessment (MoCA [®])	47
6.7.5	Unified Parkinson Disease Rating Scale (UPDRS).....	47

6.7.6	Barnes Akathisia Rating Scale (BARS).....	47
6.7.7	Epworth Sleepiness Scale (ESS).....	47
6.7.8	Swallowing Disturbance Questionnaire (SDQ).....	47
6.8	Efficacy and Quality of Life Measures	48
6.8.1	UHDRS - Total Maximal Chorea Score (TMC).....	48
6.8.2	Patient Global Impression of change (PGIC)	48
6.8.3	Clinical Global Impression of Change (CGIC)	48
6.8.4	Short Form 36 Health Survey (SF-36).....	48
6.8.5	Berg Balance Test (BBT).....	48
6.8.6	Independent Rating of Chorea	48
6.9	Pharmacokinetic Evaluations	49
6.10	Subject Restrictions.....	49
6.10.1	Concomitant Medications	49
6.10.2	Use of Alcohol or Sedating drugs.....	50
6.10.3	Other Restrictions	50
6.11	Caregiver Responsibilities.....	50
6.12	Capacity Assessment.....	51
6.13	Withdrawal Criteria.....	51
6.14	Discontinued Subjects	51
6.15	Study Termination.....	52
7	ADVERSE EVENTS	52
7.1	Definitions.....	52
7.1.1	Adverse Event.....	52
7.1.2	Suspected Adverse Reaction.....	53
7.1.3	Adverse Reaction	53
7.1.4	Unexpected Adverse Event.....	53
7.1.5	Serious Adverse Event (SAE).....	54
7.2	Recording of Adverse Events.....	54
7.2.1	Recording of Non-Serious Adverse Events (AEs).....	55
7.2.2	Recording of Serious Adverse Events (SAEs).....	55
7.3	Evaluation of Adverse Events (Serious and Non-Serious)	55
7.3.1	Severity	56
7.3.2	Relationship to Study Drug.....	56

7.3.3	Action Taken with Study Treatment.....	56
7.3.4	Treatment Required	57
7.3.5	Outcome.....	57
7.4	Procedures for Reporting Serious Adverse Events	57
7.4.1	Completion and Transmission of the SAE Report.....	57
7.4.2	Regulatory Reporting Requirements for SAEs.....	58
7.5	Procedures for Reporting Pregnancy Exposure and Birth Events.....	58
8	STATISTICAL PROCEDURES AND DATA ANALYSIS	58
8.1	Analysis Populations	58
8.2	Demographics and Baseline Data	59
8.3	Efficacy Analysis	59
8.3.1	Primary Efficacy Analysis	59
8.3.2	Analysis of Key Secondary Endpoints	59
8.3.3	Analysis of Additional Secondary Endpoints.....	60
8.3.4	Sample Size Considerations.....	60
8.4	Safety Analyses	60
8.5	Safety Endpoints	61
8.6	Pharmacokinetics	61
8.7	Protocol Deviations and Violations.....	61
8.8	Data Recording.....	61
8.9	Data Quality Assurance.....	62
8.10	Data Management	62
9	ADMINISTRATIVE ISSUES.....	62
9.1	Investigator Obligations	62
9.1.1	Independent Ethics Committee (IEC)/Institutional Review Board (IRB) Approval	62
9.1.2	Written Informed Consent	62
9.1.3	Emergency Contact with Investigator.....	63
9.1.4	Ethical Considerations	63
9.1.5	Privacy Rule.....	63
9.2	Protocol Amendments	64
9.3	Records Retention	64
9.4	Study Monitoring	64
9.4.1	Steering Committee	65

9.4.2	Medical Monitoring	65
9.4.3	Safety Monitoring Committee (SMC)	65
9.5	Quality Assurance	66
10	INFORMATION DISCLOSURE AND INVENTIONS.....	66
10.1	Ownership	66
10.2	Confidentiality.....	66
10.3	Publication.....	66
11	REFERENCES	68
12	APPENDICES.....	70

LIST OF APPENDICES

Appendix 1: Site Investigator Signature Page	71
Appendix 2: Unified Huntington Disease Rating Scale (UHDRS)	72
Appendix 3: Hospital Anxiety and Depression Scale (HADS)	88
Appendix 4: Columbia Suicidality Severity Rating Scale (C-SSRS) – Baseline	90
Appendix 5: Columbia Suicidality Severity Rating Scale (C-SSRS) – Since Last Visit	94
Appendix 6: Unified Parkinson Disease Rating Scale (UPDRS): Speech	98
Appendix 7: Montreal Cognitive Assessment (MoCA [®])	99
Appendix 8: Epworth Sleepiness Scale (ESS).....	103
Appendix 9: Barnes Akathisia Rating Scale (BARS).....	105
Appendix 10: Short Form 36 Health Survey (SF-36).....	108
Appendix 11: Patient Global Impression of Change (PGIC).....	115
Appendix 12: Clinical Global Impression of Change (CGIC).....	116
Appendix 13: Berg Balance Test (BBT).....	117
Appendix 14: Swallowing Disturbance Questionnaire (SDQ).....	125
Appendix 15: Protocol for Video Recording Chorea	127
Appendix 16: Strong CYP2D6 Inhibitors.....	128
Appendix 17: Prohibited or Restricted QT Prolonging Drugs.....	129
Appendix 18: Prohibited Antipsychotic Drugs.....	130
Appendix 19: Celexa and Lexapro (Cipralext) Dosing Information	131

LIST OF ABBREVIATIONS

Abbreviation	Definition
≤	Less than or equal to
≥	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
CGIC	Clinical Global Impression of Change
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 Coordinating 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

Abbreviation	Definition
EU	European Union
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	Lactase 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
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic

Abbreviation	Definition
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
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
SMC	Safety Monitoring Committee
SSRI	Selective serotonin reuptake inhibitor
TMC	Total maximal chorea score
TFC	Total functional capacity
t_{\max}	Time of maximum drug concentration
UHDRS	Unified Huntington 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 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-dihydrotetrabenazine (α -HTBZ) and beta-dihydrotetrabenazine (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 a 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 form of tetrabenazine (referred to as SD-809) which is eliminated more slowly than tetrabenazine and is 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 (d₆-Tetrabenazine)

SD-809 is a deuterated form 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 respective 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 d₆-α-HTBZ and d₆-β-HTBZ. Peak plasma concentrations of the active moieties d₆-α-HTBZ and d₆-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 d₆-(α+β)-HTBZ.

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 AE profile of SD-809 was comparable 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.

2 STUDY OBJECTIVES

The objectives of this study are:

- To evaluate the efficacy of SD-809 ER to reduce the chorea associated with HD
- To evaluate the safety and tolerability of titration and maintenance therapy with SD-809 ER

3 INVESTIGATIONAL PLAN

This is a randomized, double blind, placebo controlled, parallel group study designed to evaluate the efficacy, safety and tolerability of SD-809 ER for the treatment of chorea associated with HD. Approximately 90 subjects will be randomized (1:1) into the study, with approximately 45 subjects receiving SD-809 ER and 45 subjects receiving placebo. The study will be conducted at approximately 30 centers in the U.S. and Canada. The study is divided into a screening period, a titration period, a maintenance period and a post-treatment safety follow up period. For subjects who complete the study, overall study participation will be up to 20 weeks.

3.1 Study Design

This is a randomized, double blind, placebo controlled parallel group study in which subjects with chorea associated with HD will be invited to participate. Subjects will undergo an independent evaluation to determine their capacity to provide informed consent. Subjects who qualify for the study will be randomized to receive either SD-809 ER or placebo in a 1:1 (SD-809 ER to placebo) ratio and the randomization will be stratified by prior exposure to tetrabenazine (previously exposed versus not previously exposed to tetrabenazine). Subjects will be titrated to an optimal dose level of study drug, followed by maintenance therapy at that dose. The overall treatment period will be 12 weeks in duration. The titration period will last 8 weeks, the maintenance period will be 4 weeks, followed by a washout period of 1 week.

Screening period (up to 4 weeks): Subjects will undergo an independent evaluation by a qualified healthcare provider to determine their capacity to provide informed consent. After informed consent is obtained, subjects who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history, physical and neurological examination, laboratory testing, 12-lead ECG, and scales to evaluate HD. Subjects will return to the clinic for a Baseline evaluation on Day 0 to re-confirm eligibility. Subjects who remain eligible for participation in the study will be randomized and will initiate therapy with either SD-809 ER or placebo on the day after the Baseline visit (Day 1). For all visits in the screening period, subjects will be required to be accompanied by a caregiver. If the capacity assessment deems the subject not able to sign consent, the legally authorized representative will also need to accompany the subject at the visit requiring signing of consent and subject assent.

Titration period (8 weeks): All subjects and caregivers will interact weekly with the clinical site, either by telephone contact or clinic visit, through Week 8 of the titration period, in order to evaluate safety and establish a dose of study drug that adequately controls chorea and is well-tolerated. Safety evaluations during titration include Unified Huntington Disease Rating Scale (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[®], Ciprallex[®]) will have additional ECGs during the titration period as specified in the Schedule of Events.

In person study visits will be scheduled at Weeks 2, 4, and 6 after initiating therapy and telephone contacts will be scheduled for Weeks 1, 3, 5, 7 and 8 after initiating therapy. 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 increased on a weekly basis 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. Although dose adjustments may be made up to and including Week 7, if a subject reaches a stable dose before Week 7, the subject will continue on that dose for the duration of the titration period and through the maintenance period. Once adequate control of chorea has been achieved, the dose of study drug should not be increased further. If a subject experiences a “clinically significant” 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 and caregiver’s reports of adverse events and chorea control, the clinical assessment of safety and efficacy by the investigator, as well as information from rating scales including the Unified Huntington Disease Rating Scale (UHDRS), the Hospital Anxiety and Depression Scale (HADS), the Swallowing Disturbance Questionnaire (SDQ), the Unified Parkinson’s Disease Rating Scale (dysarthria item) (UPDRS [dysarthria]), the Barnes Akathisia Rating Scale (BARS), the Epworth Sleepiness Scale (ESS), and the Columbia Suicide Severity Rating Scale (C-SSRS). At the end of the titration period, the subject’s dose will be established for the maintenance period.

Maintenance period (4 weeks): Subjects will continue to receive their maintenance dose over the next 4 weeks (dose reductions for adverse events are allowed) and will return for in person visits at Weeks 9 and 12 for evaluation of safety, efficacy and pharmacokinetics. In addition, there will be a telephone contact at Week 10 to evaluate safety. At the end of the maintenance period (Week 12), subjects will undergo a complete evaluation, including physical and neurological exam, safety labs and 12-lead ECG and performance of all rating scales. If a subject requires a dose reduction based on a telephone contact during the maintenance period, an unscheduled clinic visit should be conducted.

Washout (1 week): All subjects will discontinue study drug after the Week 12 visit and will return at Week 13 for evaluation of safety, chorea and motor function. Subjects who complete the study and were tolerating study drug may be eligible to participate in a long term safety study of SD-809 ER.

¹ See [Section 7](#) for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

Subjects not participating in the long term safety study of SD-809 ER will have a follow up telephone contact at Week 16, four weeks after their last dose of study drug.

3.2 Rationale for Study Design

The study is designed to evaluate the efficacy, safety and tolerability of SD-809 ER compared to placebo in subjects with Huntington chorea.

In order to characterize the efficacy and safety initiating treatment with SD-809 ER in the target population, subjects who have not been exposed to tetrabenazine in the 6 months prior to Screening will be enrolled into the study. As with tetrabenazine therapy, study drug should be titrated over several weeks in order to identify a dose that reduces chorea and is well-tolerated. To accomplish this, subjects will begin a low dose of study drug and undergo evaluation on a weekly basis for chorea control, adverse events, and possible dose adjustment. In addition to the subject's assessment, caregiver's and investigator's assessments of chorea control and tolerability, 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.** Subjects will continue their dose established during titration into the maintenance period.

The present investigation is randomized, double blind, and placebo controlled and as such is optimally designed to characterize the efficacy and adverse event profile of 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. In the present study, CYP2D6 genotyping will be performed in a blinded manner to allow evaluation of the effect of phenotype on safety and efficacy 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 delivers an AUC of total (α + β)-HTBZ that is comparable to 12.5 mg 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 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 label. Weekly dose adjustments for insufficient chorea control will be limited to increments of 6 mg per day and total daily dose levels of 12 mg and higher will be administered in two divided doses. The maximum total daily dose of SD-809 ER is 48 mg per day, unless the subject is receiving a strong CYP2D6 inhibitor (e.g., paroxetine, see [Appendix 16](#)), in which case the maximum total daily dose is 36 mg.

4 STUDY POPULATION

4.1 Population Characteristics

Male and female adult subjects with manifest HD and chorea who have not been exposed to tetrabenazine will be enrolled into the study.

4.2 Inclusion Criteria

1. Subject is at least 18 years of age or the age of majority (whichever is older) at Screening.
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 has a Total Maximal Chorea Score (TMC) ≥ 8 at Screening and Baseline.
(Note: The Baseline TMC may be < 8 if the average of the Screening and Baseline scores is ≥ 8 and the difference between the Screening and Baseline scores is no more than 4).
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. Female subjects of childbearing potential² 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 enrollment.
 - Stable hormonal contraception (with approved oral, transdermal, or depot regimen) for at least 3 months prior to screening.
8. 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.

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 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 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.

- 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 Screening, Baseline and Weeks 4, 9 and 12 Visits. Caregivers will be encouraged to attend other visits.
9. 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).

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 16](#) 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 Screening or Baseline.
5. Subject has an unstable or serious medical or psychiatric illness at Screening or Baseline.
6. Subject has received tetrabenazine within 6 months prior to Screening.
7. Subject has received any of the following concomitant medications within 30 days of Screening or Baseline:
 - Antipsychotics (See [Appendix 18](#))
 - Metoclopramide
 - Monoamine oxidase inhibitors (MAOI)
 - Levodopa or dopamine agonists
 - Reserpine
 - Amantadine
 - Memantine
8. Subject has a score of ≥ 11 on the Swallowing Disturbance Questionnaire (SDQ) at

Screening.

9. Subject has a Unified Parkinson's Disease Rating Scale (UPDRS) dysarthria score of ≥ 3 at Screening.
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 19](#) for Celexa and Lexapro (Cipralex) dosing information
 - See [Appendix 17](#) 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 medical monitor.
 - Note: Subjects with abnormalities in two or more of these analytes (AST, ALT, ALP, TBil) must be approved by the medical 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 within 30 days (or 5 drug half-lives) of Screening, whichever is longer.
16. Subject is pregnant or breast-feeding at Screening or Baseline.

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 18](#)):

- 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.

17. Subject acknowledges present use of illicit drugs at Screening.
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.

5 STUDY TREATMENT

The study medication to be used in this trial is an extended release (ER) formulation of SD-809 or placebo. Three dose strengths of SD-809 ER will be available for use: 6, 9, and 12 mg tablets. All tablets (SD-809 ER or placebo) are identical in size and color (white). Thus, the actual dose of SD-809 received by the subject will be determined by the clinical pack supplied. The initial drug supply will be provided in the clinic at the Baseline visit.

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 white polymer coating to aid in swallowing. SD-809 ER and placebo tablets have been manufactured according to current Good Manufacturing Practices regulations. SD-809 ER tablets, or their placebo, will be supplied as 6, 9, and 12 mg tablets and will be packaged in blister packs and labeled according to applicable regulatory guidelines. Each blister pack will contain a sufficient supply of drug until the next specified visit/telephone contact, plus overage to account for potential delays in study visits or evaluations or receipt of their supplies.

Placebo tablets for SD-809 ER are composed of the same excipients as SD-809 ER.

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 Blinding

During the treatment period the sponsor, subjects as well as the investigators and their site personnel will be blinded to treatment assignment. Active and placebo investigational product will be identical in appearance and packaged in investigational product kits according to the randomization code by an independent vendor selected by the sponsor.

5.3 Randomization to Study Drug

Subjects who meet all selection criteria and complete all baseline assessments will be randomized to receive either SD-809 ER (or placebo) tablets using a 1:1 allocation ratio. The randomization will be stratified by prior exposure to tetrabenazine (previously exposed versus not previously exposed to tetrabenazine). Randomization and stratification will be performed through the Interactive Web Response System (IWRS).

Following completion of all baseline assessments, an authorized staff member will submit all required documentation to the Clinical Trials Coordinating Center (CTCC) in order to obtain an approval code for randomization. Using the approval code, the authorized staff member will randomize the subject through IWRS at Visit 2/Baseline. Complete instructions for randomization of subjects will be provided in the study operations manual.

5.4 Unblinding During the Study

The blind may be broken in the event of a medical emergency, in which knowledge of the

study medication identity is critical to the management of the subject. Before breaking the blind the investigator should determine that the information is necessary (i.e., that it will alter the subject's immediate course of treatment). In many cases, particularly when the emergency is clearly not study medication-related, the problem may be effectively managed by assuming that the subject is receiving active study medication without the need for unblinding.

If the study site deems it necessary to break the blind for a study subject, an attempt to contact the Medical Monitor will be made to obtain concurrence. If it is not possible to contact the Medical Monitor beforehand, the site personnel will contact him/her as soon as possible after breaking the blind for a subject.

If a determination has been made that a subject's treatment needs to be unblinded, the date of unblinding, the reason for unblinding and the initials of the investigational center staff member who performed the unblinding will be recorded. Unblinding will be performed via the IWRS system according to procedures in the study operations manual.

Any subject whose blind has been broken must be discharged from the study.

5.5 Treatment Regimen

For all subjects, study medication should be dosed as follows:

- All treatment regimens will be administered twice daily with meals, approximately 10 hours apart during the day.
- The starting dose will be SD-809 ER 6 mg or placebo in the AM; both treatment arms will receive placebo in the PM
- The dose of SD-809 ER (or placebo) may be adjusted weekly in increments of 6 mg per day (SD-809 ER or placebo) during the titration period to identify a dose level that reduces chorea and is well-tolerated.
 - Dose reductions are also in increments of 6 mg per day
- The maximum total daily dose of SD-809 ER is 48 mg (24 mg BID), unless the subject is receiving a potent CYP2D6 inhibitor (See [Appendix 16](#)), in which case the maximum total daily dose is 36 mg
 - Individual doses of 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.
- 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.

The following table summarizes the dose levels and tablet numbers by dose for SD-809 ER treatment; placebo subjects will receive tablets identical in appearance:

Dose Level	Total Daily Dose	Morning Dose	Evening Dose
1	6 mg	6 mg	Placebo
	Tablets	1 x 6 mg	1 x Placebo tablet
2	12 mg	6 mg	6 mg
	Tablets	1 x 6 mg	1 x 6 mg
3	18 mg	9 mg	9 mg
	Tablets	1 x 9 mg	1 x 9 mg
4	24 mg	12 mg	12 mg
	Tablets	1 x 12 mg	1 x 12 mg
5	30 mg	15 mg	15 mg
	Tablets	1 x 9 mg and 1 x 6 mg	1 x 9 mg and 1 x 6 mg
6	36 mg	18 mg	18 mg
	Tablets	2 x 9 mg	2 x 9 mg
7	42 mg	21 mg	21 mg
	Tablets	1 x 12 mg and 1 x 9 mg	1 x 12 mg and 1 x 9 mg
8	48 mg	24 mg	24 mg
	Tablets	2 x 12 mg	2 x 12 mg

Note: SD-809 ER Dose strengths include 6, 9, and 12 mg tablets.

5.6 Titrating Study Medication

According to the guidance in [Section 6.2](#), the investigator will titrate the dose of study drug (SD-809 ER or placebo) to a level in which adequate chorea control has been achieved and the patient is tolerating the treatment regimen or until the maximum permitted dose 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, the dose of SD-809 ER may be increased on a weekly basis.

Dose increases are limited as follows:

- May occur no more frequently than once per week during the Titration Period (Note: Based on visit windows, at least 5 day must elapse between dose increases).
- Dose increase is limited to 6 mg/day (each week).

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

¹ See [Section 7](#) for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

5.6.1 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.

A dose reduction of 6 mg/day can be made (via IWRS) by requesting that the next lowest dose level be shipped directly to the subject. If a subject requires a dose reduction based on telephone contact during the maintenance period, an unscheduled clinic visit should be conducted.

Suspension of study medication for up to one week, if warranted, is allowed. If the subject restarts study medication within 7 days of suspension, the full dose of SD-809 ER may be resumed without titration. **Suspensions of study medication for adverse events must be reviewed with the Medical Monitor before therapy is restarted. Similarly, suspensions for more than 7 days must be reviewed by the Medical Monitor to determine if there is adequate time for subjects to be re-titrated and complete evaluations.**

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

If a subject has a dose reduction or suspension, efficacy evaluations should not be performed for at least 5 days after the change.

5.7 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.

5.8 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 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 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 at the

end of the study by the study monitor. When requested in writing by the Sponsor, returned and unused drug supplies may be destroyed by the Investigator provided such disposition does not expose humans to risks from the drug. 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.

5.9 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 (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% to 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)

See the Schedule of Events 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 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 volunteer 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.

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 Coordinating 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 patients 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 a subject signs the informed consent to obtain the CTCC unique ID, he/she will be directed to a secure website where he/she or the site Study Coordinator (if the patient requests/prefers) will enter the patient'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 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. Screening procedures will consist of the following:

- Complete medical history including demographics, concomitant medications (including over the counter and herbals) and alcohol use
- 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: CAG repeat
- 12- lead ECG
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Baseline version
- Unified Huntington Disease Rating Scale (UHDRS):
 - Motor
 - TFC
- Video recording of Chorea (See [Section 6.8.6](#) and [Appendix 15](#) for recording protocol.)
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item

- Swallowing Disturbance Questionnaire (SDQ)
- Eligibility data will be reviewed by the medical monitor to determine if the subject may progress to randomization at the Baseline visit. (See Operations manual).

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 Baseline Visit (Day 0)

See the Schedule of Events 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. Baseline visit activities will consist of the following:

- Physical examination, vital signs (including orthostatic blood pressure and pulse) and weight
- Assess adverse events and concomitant medication use
- Clinical laboratory tests: serum chemistry, hematology, and urinalysis
- Urine pregnancy test (women of child-bearing potential only)
- Blinded CYP2D6 genotype blood sampling
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Montreal Cognitive Assessment (MoCA[®])
- Complete Unified Huntington Disease Rating Scale (UHDRS):
 - Motor
 - Cognition
 - Behavior
 - Functional assessment
 - Independence
 - TFC
 - Summary

- Video recording of Chorea (See [Section 6.8.6](#) and [Appendix 15](#) for recording protocol.)
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Short Form 36 health survey (SF-36)
- Berg Balance Test (BBT)
- Swallowing Disturbance Questionnaire (SDQ)
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Baseline results will be assessed by the Investigator or Sub-Investigator and subjects who meet eligibility criteria will be enrolled into the study.
- Randomize subject and dispense SD-809 ER (or placebo) via IWRS: Subjects will be supplied with one week of study medication.
- Week 1 telephone contact will be scheduled.

6.2 Titration Period

All subjects will interact weekly with the clinical site, either by telephone contact or clinic visit, through Week 8 of the 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, CipraleX) will have additional ECGs during the titration period as specified in the Schedule of Events. The investigator, in consultation with the subject and caregiver, will determine when an adequate level of chorea control has been achieved. 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, the dose of SD-809 ER may be increased on a weekly basis. Although dose adjustments may be made up to and including the Week 7 visit, if a subject reaches a stable dose before that Week 7, the subject will continue on that dose through the maintenance period.

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. Telephone contacts will be scheduled for Weeks 1, 3, 5, 7 and 8 after initiating therapy

¹ See [Section 7](#) for evaluation of AEs regarding severity, relationship to study drug and definition of SAE.

and clinic visits will be scheduled at Weeks 2, 4, and 6 after initiating therapy. At the end of the titration period, the subject's dose will be established for the maintenance period. Dose reductions during the maintenance period are allowed only for adverse events.

6.2.1 Telephone Contacts (Week 1 [± 1 day] and 3, 5, and 7 [all ± 3 days])

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

Subjects will be contacted by telephone during Weeks 1, 3, 5 and 7 of the titration period for evaluation of their current dose of study drug.

Telephone contact assessments will include:

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

6.2.2 Clinic Visits (Weeks 2, 4, and 6 [all ± 3 days])

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

Clinic visits will be scheduled at Weeks 2, 4 and 6 of the titration period.

Evaluations will include the following activities:

- Assessment of adverse events, chorea control (in consultation with the subject and caregiver), and concomitant medication use
- Vital signs (at Week 4 only, include orthostatic blood pressure and pulse)
- Weight
- Clinical laboratory tests (Week 4 only): serum chemistry, hematology, and urinalysis
- For subjects on allowed doses of citalopram (Celexa) or escitalopram (Lexapro, Cipralex);
 - At Week 2: Perform a 12-lead ECG
 - At Week 4 and Week 6: Perform a 12-lead ECG if the dose of study drug has been increased since the last ECG was collected
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Unified Huntington Disease Rating Scale (UHDRS)
 - Motor
 - Behavior (Weeks 2 and 4 only)
 - Cognition (Week 4 only)
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item

- Berg Balance Test (BBT)
- Montreal Cognitive Assessment (MoCA[®]) (Week 4 only)
- Swallowing Disturbance Questionnaire (SDQ)
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Patient Global Impression of Change (Week 4 only)
- Clinical Global Impression of Change (Week 4 only)
- Evaluation 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 compliance
- IWRS will be contacted to re-order study medication (Note: If the visit occurs such that re-dispensing of study drug cannot occur in time to be received by the following day, study drug remaining from the prior week may be re-dispensed if the patient is not undergoing a dose reduction. In this case, instruct the subject to take study drug from the prior week's package until the new package of study drug is received.)
- Next telephone contact and visit will be scheduled/reconfirmed

6.2.3 Telephone Contact (Week 8 ± 3 days)

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

Subjects will be contacted by telephone during Week 8 to assess adverse events (in consultation with the subject and caregiver) and concomitant medications use and to schedule/confirm the next visit.

Remind subjects 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 next clinic visit.

IWRS will be contacted to re-order study medication.

6.3 Maintenance Period

Subjects will continue to receive their maintenance dose after the Week 8 telephone contact (dose reductions for adverse events are allowed) and will return for in person visits at Weeks 9 and 12 for evaluation of safety, efficacy and blood sampling for pharmacokinetics. At the end of the maintenance period (Week 12), subjects will undergo a comprehensive evaluation, including physical and complete neurological exam, safety labs and 12-lead ECG and performance of all rating scales. If a subject requires a dose reduction based on telephone contact during the maintenance period, an unscheduled clinic visit should be conducted.

6.3.1 Clinic Visit (Week 9 ± 3 days)

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

The Week 9 clinic visit includes 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 if the dose of study drug has been increased since the last ECG was collected
- PK blood sampling
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Unified Huntington Disease Rating Scale (UHDRS)
 - Motor
 - Cognition
 - Behavior
- Video recording of Chorea (See [Section 6.8.6](#) and [Appendix 15](#) for recording protocol.)
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Montreal Cognitive Assessment (MoCA[®])
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Berg Balance Test (BBT)
- Swallowing Disturbance Questionnaire (SDQ)
- Patient Global Impression of Change (PGIC)
- Clinical Global Impression of Change (CGIC)
- Assessment of medication compliance
- IWRS will be contacted to re-order study medication for the remainder of the Maintenance Period
- Next telephone contact and visit will be scheduled/reconfirmed

6.3.2 Telephone Contact (Week 10 ± 3 days)

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

Subjects will be contacted by telephone during Week 10 to assess adverse events (in consultation with the subject and caregiver) and concomitant medications use and to schedule/confirm the next visit.

Remind subjects 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 next clinic visit.

6.3.3 Clinic Visit (Week 12 ± 3 days or Early Termination)

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

All subjects will stop study drug after the week 12 visit. Subjects will return to the clinic for the following Week 12 end of maintenance period assessments:

- Assessment of adverse events (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, and urinalysis
- 12-lead ECG
- PK blood sampling (*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.*)
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Montreal Cognitive Assessment (MoCA[®])
- Unified Huntington Disease Rating Scale (UHDRS)
 - Motor
 - Cognition
 - Behavior
 - Functional assessment
 - Independence
 - TFC
 - Summary
- Video recording of Chorea (See [Section 6.8.6](#) and [Appendix 15](#) for recording protocol.)
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Berg Balance Test (BBT)
- Swallowing Disturbance Questionnaire (SDQ)
- Patient Global Impression of Change (PGIC)
- Clinical Global Impression of Change (CGIC)
- Short Form 36 health survey (SF-36)

- Assessment of medication compliance and collection of all study medication
- If not an Early Termination visit, the next 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 the Schedule of Events.

6.4 Post-Treatment Safety Follow Up

All subjects will discontinue study drug after the Week 12 visit and will return one week later for evaluation of safety, chorea and motor function. Subjects who complete the study (i.e., the Week 13 Visit) and are tolerating study drug may be eligible to participate in a long term safety study of SD-809 ER. Subjects not participating in the long term safety study of SD-809 ER will have a follow up telephone contact four weeks after their last dose of study drug.

6.4.1 Clinic Visit (Week 13 ± 3 days)

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

All subjects will return one week after the Week 12 visit for evaluation of safety, chorea and motor function. The following activities should be performed:

- Assessment of adverse events (in consultation with the subject and caregiver) and concomitant medication use
- Vital signs and weight
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Unified Huntington Disease Rating Scale (UHDRS)
 - Motor
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Berg Balance Test (BBT)
- Swallowing Disturbance Questionnaire (SDQ)

Subjects who complete the study and were tolerating study drug may be eligible to participate in a long term safety study of SD-809 ER. For those subjects not participating in the long term safety study, schedule the Week 16 telephone contact.

6.4.2 Telephone Contact (Week 16 ± 3 days)

Subjects not participating in the long term safety study of SD-809 ER will have a follow up telephone contact three weeks after the Week 13 visit (four weeks after their last dose of study medication (Week 12)). 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 for a detailed summary of activities.

For unscheduled clinic visit(s) needed 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 medication use
- Brief physical examination (at the Investigator's discretion)
- Complete neurological examination (at the Investigator's discretion)
- Vital signs and weight
- 12-lead ECG (at the Investigator's discretion)
- Clinical laboratory tests: serum chemistry, hematology, and urinalysis (at the Investigator's discretion)
- PK Blood Sampling (single blood sample for Unscheduled Visits due to SAE, if within 48 hours)
- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS): Since Last Visit version
- Unified Huntington Disease Rating Scale (UHDRS)
 - Motor
- Unified Parkinson's Disease Rating Scale (UPDRS): dysarthria item
- Berg Balance Test (BBT)
- Barnes Akathisia Rating Scale (BARS)
- Epworth Sleepiness Scale (ESS)
- Swallowing Disturbance Questionnaire (SDQ)

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 and recorded in the electronic Case Report Form (eCRF).

6.6.2 *Physical Examination*

A complete physical examination will be performed as specified in the SCHEDULE OF EVENTS. 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
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* 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. 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
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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 4 (titration) and Week 12/ET (maintenance).

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 • Prothrombin Time (PT w/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 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 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.

6.7.5 Unified Parkinson 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 patients 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 patients with dysphagia that had underlying pathology confirmed on fiberoptic endoscopic evaluation of swallowing (FEES) (21).

6.8 Efficacy and Quality of Life Measures

6.8.1 UHDRS - Total Maximal Chorea Score (TMC)

The motor assessment (Part 1) of the UHDRS includes 15 items that assess the motor status of the subject, including chorea. Other assessments include: Ocular pursuit, saccade initiation and velocity, dysarthria, tongue protrusion, gait, tandem walking and maximal dystonia.

The maximal chorea score is determined from Item 12 of Part 1, and quantifies chorea based on assessments of the face, bucco-oral-lingual area, trunk, and the four extremities. The minimum score is zero (absent) and the maximal score is to 28 (17).

6.8.2 Patient Global Impression of change (PGIC)

The Patient Global Impression of Change is single item questionnaire that asks the patient to assess their HD symptoms at specific visits after initiating therapy. The PGIC uses a 7-point Likert Scale, ranging from very much worse (−3) to very much improved (+3), to assess overall response to therapy. In general, patient-rated global measures of change have face validity and have been shown to correlate with disability for a number of chronic conditions (22).

6.8.3 Clinical Global Impression of Change (CGIC)

The Clinical Global Impression of Change is single item questionnaire that asks the investigator to assess a subject's HD symptoms at specific visits after initiating therapy. The CGIC uses a 7-point Likert Scale, ranging from very much worse (−3) to very much improved (+3), to assess overall response to therapy.

6.8.4 Short Form 36 Health Survey (SF-36)

The SF-36 is a short-form health survey with 36 questions used to evaluate health-related quality of life (23). It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 has been useful in comparing general and specific populations and comparing the relative burden of various diseases, and for screening individual patients. The SF-36 has been evaluated in HD patients and shown to have robust construct validity and test–retest reliability and was also able to discriminate from age-matched controls and normative data on the 10 item physical functioning sub-scale scale (24). Version 2 of the SF-36 will be used in the study (25).

6.8.5 Berg Balance Test (BBT)

The Berg Balance Test (BBT) is a 14-item assessment of sitting, standing, transferring, and turning. Each task is rated on a scale of 0–4 (range 0–56, high score is normal). This scale has been validated in an elderly population and in acute stroke and has been shown to improve in patients with chorea associated with HD who are receiving tetrabenazine (26).

6.8.6 Independent Rating of Chorea

To enable an independent rating of chorea, a limited motor examination will be videotaped using a standard protocol at Screening, Baseline and at Weeks 9 and 12 (See [Appendix 15](#)). Videos will be recorded in a blinded manner with respect to visit number, site and date of recording.

Videos will independently rated by an expert in Huntington disease to provide an assessment of chorea that is not influenced by patient reports of tolerability or efficacy and will be used to support the primary analysis based on the examination at the investigative site.

6.9 Pharmacokinetic Evaluations

Blood samples will be obtained for measurement of plasma concentrations of alpha-dihydrotrabenazine (α -HTBZ), beta-(β)-HTBZ, total (α + β)-HTBZ and other metabolites, as required. At the Week 9 and Week 12 Visits, subjects will have blood sampling for PK as follows:

- Week 9:
 - Sample 1 upon arrival at clinic and
 - Sample 2 at least 2 hours after sample 1.
- Week 12:
 - Sample 1 upon arrival in clinic and
 - Sample 2 at least 3 hours after sample 1.
- Note: The time between samples should be maximized in order to provide the most useful information.

At each timepoint, 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 degrees °C or below.

Subjects will be provided with a diary to record meal and dosing times on PK sampling days during maintenance only. Prior to clinic visits on Weeks 9 and 12 (Visits 6 and 7), 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. Subjects should take their usual morning dose of study drug at home and have initial blood sampling for PK in clinic on these visits.

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.

6.10 Subject Restrictions

6.10.1 Concomitant Medications

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

- Antipsychotics (see [Appendix 18](#))
- Metoclopramide
- MAO Inhibitors

- Levodopa or dopamine agonists
- Reserpine
- Amantadine
- Memantine

Subjects discontinuing anti-psychotics (See [Appendix 18](#)) 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 17](#)) should not be taken concomitantly with study medication. A washout period of 5 half-lives is recommended or other duration as approved by the Medical 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.

6.10.2 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.

6.10.3 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 and throughout study participation.

6.11 Caregiver Responsibilities

Each subject participating in the study must have a reliable caregiver. **Subjects with a TFC score of 5-7 at Screening must have a live-in 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.

Subjects with a TFC score of 5-7 at Screening, or those who enrolled with the consent of a legally authorized representative, must have the caregiver present at all study visits.

For subjects with a TFC score of 8-13 at Screening who did not require a legally authorized representative to provide informed consent:

- The caregiver must attend the following visits: Screening, Baseline and Weeks 4, 9 and 12.
- For the Week 2, 6, and 13 visits, the caregiver is encouraged to be present at these study visits. However, if attendance at the Week 2, 6 or 13 visit is not feasible, the caregiver must be available by telephone at the time of the visit.

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.

6.12 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.

6.13 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 Medical 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 Medical 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 patient 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.

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 Medical Monitor's opinion may be sought in those cases in which the site investigator is unable to make an independent judgment. The Medical 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 5.6.1](#) for guidance in contacting medical 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 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

Intent to Treat Population: The Intent to Treat (ITT) population will include all randomized subjects. In analyses and summaries based on the ITT population, subjects will be included in the treatment group to which they were randomized, regardless of the treatment that was actually received.

Modified Intent to Treat Population: The modified intent to treat (mITT) population will include all subjects in the ITT population who were randomized to treatment, received study drug and had at least one post-baseline assessment of the TMC. The primary efficacy analysis will be completed on the mITT population. In analyses and summaries based on the mITT population, subjects will be included in the treatment group to which they were randomized, regardless of the treatment that was actually received.

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. In analyses and summaries based on the Safety population,

subjects will be included in the treatment group based on the treatment actually received. If relevant, details of their participation and reason for withdrawal will be listed separately in the study report.

8.2 Demographics and Baseline Data

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

8.3 Efficacy Analysis

8.3.1 Primary Efficacy Analysis

The primary efficacy endpoint for this study is the change in Total Maximal Chorea Score (TMC) from Baseline (defined for each subject as the average of values from the Screening and Day 0 visits) to maintenance therapy (defined for each subject as the average of values from the Week 9 and Week 12 visits).

The primary analysis will be carried out using an analysis of covariance (ANCOVA) model with the change from baseline in TMC as the dependent variable, treatment group and randomization stratification variable as factors, and the baseline TMC score as a covariate. The SD-809 ER and placebo groups will be compared using a two-sided test at the 5% level of significance.

8.3.2 Analysis of Key Secondary Endpoints

The following key secondary efficacy endpoints will be analyzed using a hierarchical (gatekeeping) testing procedure:

- The proportion of subjects who are a treatment success at the end of the end of therapy, based on the Patient Global Impression of Change (PGIC). A treatment success is defined as Much or Very Much Improved on the PGIC at the Week 12 visit. Subjects whose status at Week 12 is not known, as well as subjects who are not Much or Very Much Improved at the Week 12 visit, will be considered to be treatment failures. The PGIC is a 7-point Likert Scale, ranging from very much worse to very much improved ([Appendix 11](#)).
- The proportion of subjects who are a treatment success at the end of the end of therapy, based on the Clinical Global Impression of Change (CGIC). A treatment success is defined as Much or Very Much Improved on the CGIC the Week 12 visit. Subjects whose status at Week 12 is not known, as well as subjects who are not Much or Very Much Improved at the Week 12 visit, will be considered to be treatment failures. The CGIC is a 7-point Likert Scale, ranging from very much worse to very much improved ([Appendix 12](#)).
- Change in the Short Form 36 Health Survey (SF-36) Physical component summary score from Baseline to Week 12.
- Change in the Berg Balance Test (BBT) score from Baseline to Week 12

If the primary analysis is statistically significant ($p < 0.05$), then the first key secondary endpoint will be analyzed, also at the 5% level of significance (two-sided). If the first key secondary endpoint is statistically significant, then the second key secondary endpoint will be similarly

analyzed, etc. For any analysis that is not statistically significant, all subsequent analyses of key secondary endpoints will be exploratory rather than confirmatory.

The two proportion endpoints compared between groups using Pearson's chi-square test. The two quantitative endpoints will be analyzed using ANCOVA models similar to that described for the primary efficacy analysis. The baseline value of the corresponding endpoint will be included as a covariate.

8.3.3 Analysis of Additional Secondary Endpoints

The percent change in TMC from Baseline to maintenance therapy will be analyzed using an ANCOVA model similar to that described for the primary analysis. The baseline value will be included as a covariate. For each subject, the baseline value will be computed as the average of the TMC at screening and baseline and the maintenance therapy value will be computed as the average of maintenance scores from weeks 9 and 12.

All additional analyses will be completed using two-sided tests at the 5% level of significance.

To enable an independent rating of chorea, a limited motor examination will be videotaped using a standard protocol at Screening, Baseline and at Weeks 9 and 12. Chorea will be independently scored using these recordings (See [Section 6.8.6](#) and [Appendix 15](#) for recording protocol).

8.3.4 Sample Size Considerations

Given a 1:1 randomization ratio (SD-809 ER to placebo), and assuming that the standard deviation of the TMC change from Baseline to Week 12 is equal to 3.7, a sample size of 80 subjects will provide 90% power to detect a treatment difference of 2.7 units change in the total maximal chorea score. Accounting for a dropout rate of approximately 10%, 90 subjects will be enrolled.

8.4 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 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[®])
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Safety data will be summarized descriptively by treatment group. 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 treatment group. 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 by treatment group. 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 by treatment group.

8.5 Safety Endpoints

The following study endpoints will be assessed:

- Incidence of adverse events (AEs), serious AEs (SAEs), severe AEs, drug related AEs, AEs leading to withdrawal, AEs during titration and AEs during maintenance therapy
- Observed values and changes in clinical laboratory parameters (hematology, chemistry, and urinalysis)
- Observed values and changes 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, SDQ, UPDRS (dysarthria), BARS, HADS, ESS, C-SSRS, and MoCA[®]

8.6 Pharmacokinetics

A population pharmacokinetic analysis will be performed using data from all subjects to examine the pharmacokinetics of SD-809 and to explore the potential effect of various covariates on the pharmacokinetics of SD-809 and, if possible, explore the relationship between pharmacokinetics and change in TMC.

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 patients.

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 Principal 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 Principal 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 a 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 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.

Digital video data is considered identifiable data (contains faces). Subjects will be informed in writing that video data will be analyzed by specific HD experts, and may be reviewed by the study principal investigators or the FDA. Sponsor medical personnel may access video data for review and analysis; however, videos will not be used by sponsor for any commercial, advertising or promotional purposes. Copies of the digital video data compiled and held for purposes of conducting this study will be handled in the strictest confidence and stored in accordance with local data protection laws, and then will be destroyed. With specific subject written consent, a copy of these data will be kept by the Huntington Study Group in a private secure database for research and educational purposes.

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, 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 Sponsor's (or designee) monitors 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, the biostatistician, the study PI and Co-PI, an experienced HD study coordinator, a psychiatrist and a HD patient advocate.

9.4.2 Medical Monitoring

The medical monitor for the study will review blinded safety data on a monthly basis during study conduct, including aggregate laboratory and adverse event data, and laboratory alert values. The medical monitor will review all Serious Adverse Events as they are reported. In addition, the medical monitor will: Authorize randomization 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 medical monitor to:

- Review drug suspensions and dose reductions, according to the procedures outlined in [Section 5.6.1](#);
- Review all withdrawals from the study for medical reasons, as outlined in [Section 6.14](#);
- Break the blind of treatment assignment ([Section 5.4](#))

9.4.3 Safety Monitoring Committee (SMC)

An independent Safety Monitoring committee (SMC) will be established prior to study start, with an appropriate charter to direct decisions and communications, maintain a firewall to preserve the blinding and integrity of the study, and monitor the trial safety results at intervals throughout the study. The SMC will be comprised of at least two clinicians, at least one of which is involved in treating patients with HD, and a statistician not otherwise associated with the trial.

The main purpose of the SMC will be to protect the interests of the subjects enrolled in the trial. Stopping rules based on safety, if deemed necessary, will be pre-specified in the SMC charter.

The SMC will determine the data necessary for monitoring and the intervals for formal review and discussion (e.g., after certain percentage of enrolled subjects complete treatment), and this information will be specified in the SMC charter.

The SMC will make recommendations to the Steering Committee (SC) and Medical monitor as to whether the trial should continue as planned or whether modifications should be made to safety monitoring. Minutes will be kept of all meetings but those referring to unblinded data will not be made available outside of the SMC until the trial is complete.

The final decision on whether the protocol should be amended or the study should be terminated will be the responsibility of Auspex and the Steering Committee. Any decision to stop will be communicated to investigators and regulatory agencies.

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.

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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 Disease Rating Scale (UHDRS)

Appendix 15: Protocol for Video Recording Chorea

View	Time (sec)	Details
Whole Body	20	<ol style="list-style-type: none"> 1. Have the Investigator or coordinator hold up the cardstock with the video ID number for this participant assigned to this visit. 2. Have the participant sit on the exam table with their legs dangling. No shoes or socks should be on their feet. 3. Have the participant extend both their arms straight out in front of them. Have them spread their fingers and close their eyes. Now ask them to begin to count backwards from 100.
Close up of Upper Body	5	
Whole Body	20	<ol style="list-style-type: none"> 1. Sitting in a chair with feet on the floor, resting palms on arms of chair. 2. Have the participant arise from the chair and walk for 10 steps, turn around and walk back and sit down.

Video camera preparation

Make sure to check the video camera prior to starting the session. Position the camera so that the participant is in full view. Remember to move the camera as the assessment shifts if necessary.

The sound should be muted, if possible. If not muted at the time of recording, it will be muted during processing, prior to independent rating. Please leave at least 5 seconds of non-critical recording between participants (i.e., record without any activity).

- Confirm the recording has been captured and is complete before transferring for independent rating.
- Additional details about video recording can be found in the study operations manual.

Appendix 16: Strong CYP2D6 Inhibitors

Subject's receiving any of these strong CYP2D6 inhibitors will have a maximal dose of SD-809 ER of 36 mg per day (or matching placebo).

- Bupropion
- Fluoxetine
- Paroxetine

Appendix 17: 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	
Bepidil	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 19 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 19 for dosing information
Flecainide	Tambacor [®]	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	Loelco [®]	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 [®] , Sojourn [®]	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 18: Prohibited Antipsychotic Drugs

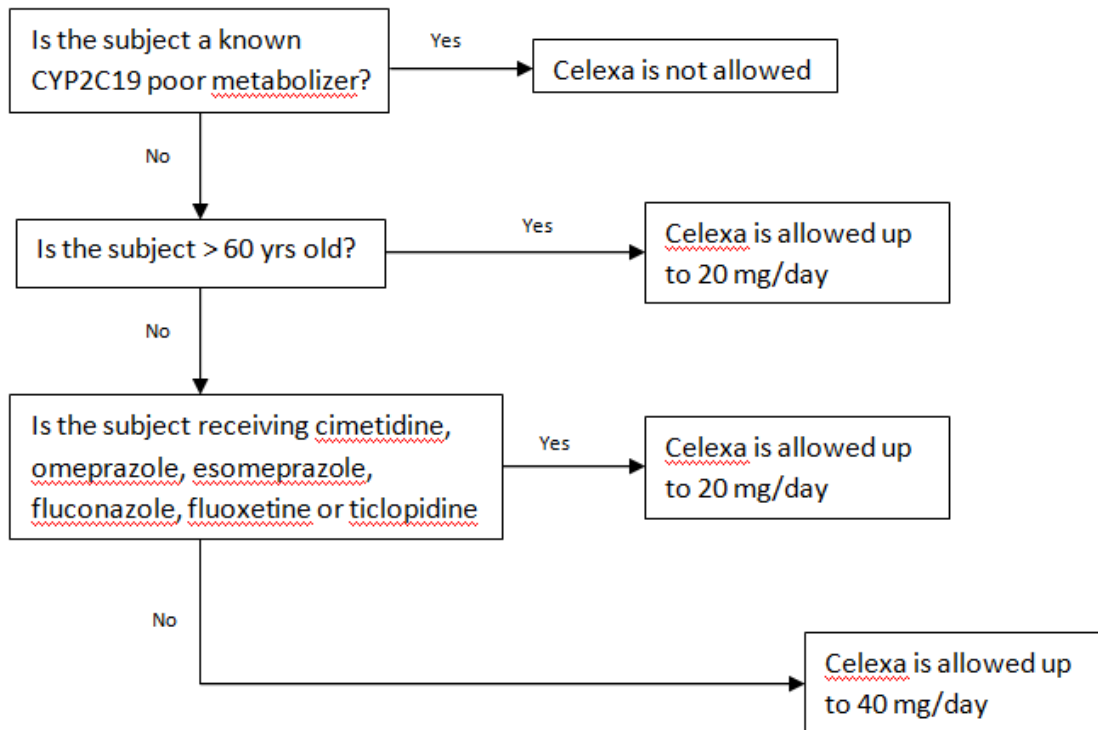
Typical/First Generation Antipsychotics	Atypical/Second Generation Antipsychotics
Chlorpromazine (Thorazine, Largactil)	Aripiprazole (Abilify)
Fluphenazine (Prolixin)	Asenapine Maleate (Saphris)
Haloperidol (Haldol, Serenace)	Clozapine (Clozaril)
Loxapine (Loxapac, Loxitane)	Iloperidone (Fanapt)
Molindone (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 19: Celexa and Lexapro (Ciprallex) 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 Ciprallex) is allowed with the following restrictions:

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