Statistical Analysis Plan

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

Study SD-809-C-16

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Date: 15 September 2017

STATISTICAL ANALYSIS PLAN

Protocol SD-809-C-16

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

Final Clinical Study Report

15 September 2017

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STATISTICAL ANALYSIS PLAN

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GLOSSARY OF TERMS

Abbreviation	Definition
AE	Adverse Event
ARC-HD	Study SD-809-C-16
ATC	Anatomical Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
BMI	Body Mass Index
CAG	Cytosine Adenine Guanine
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESS	Epworth Sleepiness Scale
ET	Early Termination
FDA	Food and Drug Administration
First-HD	Study SD-809-C-15
HADS	Hospital Anxiety and Depression Scale
HD	Huntington's Disease
HDBZ	Dihydrodeutetrabenazine
HSG	Huntington Study Group
HTBZ	Dihydrotetrabenzine
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
MoCA©	Montreal Cognitive Assessment
NDA	New Drug Application
PK	Pharmacokinetic
PR	PR interval - measured from the beginning of the P wave to the beginning of the QRS complex
QRS	QRS duration (complex) - a structure on the ECG that corresponds to the depolarization of the ventricles
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

Abbreviation	Definition
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDQ	Swallowing Disturbance Questionnaire
SOC	System Organ Class
TBZ	Tetrabenazine
TEAE	Treatment-Emergent Adverse Event
TFC	Total Functional Capacity
TMC	Total Maximal Chorea score
UHDRS	Unified Huntington Disease Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale
WHODRUG	World Health Organization drug dictionary

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for the analysis of data from Protocol SD-809-C-16, "An Open-Label, Long Term Safety Study of SD-809 ER in Subjects with Chorea Associated with Huntington Disease." All of the analyses specified in this SAP will be included in the final Clinical Study Report (CSR).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials. The following documents were reviewed in preparation of this SAP:

- Final Clinical Protocol SD-809-C-16, Amendment 03, issued 02 March 2015
- Case report forms (CRFs) for Protocol SD-809-C-16, issued 18 January, 2017

Throughout this SAP, SD-809 extended release will be denoted simply as SD-809.

2 Purpose of the Analyses

The purpose of this SAP is to outline the planned analyses to be completed to support the final Clinical Study Report (CSR) for Protocol SD-809-C-16. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

3 Study Objectives

The objectives of this study are as follows:

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

4 Study Design

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

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

Switch subjects are those subjects who are currently receiving stable doses of TBZ for treatment of chorea associated with HD and convert to SD-809 based on an algorithm designed to achieve comparable exposure to total (α+β)-dihydrotetrabenazine (HTBZ) and (α+β)-dihydrodeutetrabenzine (HDBZ) metabolites.

Rollover subjects are those subjects who have successfully completed Study SD-809-C-15 and continue on long-term SD-809 after a 1-week washout period.

Subjects Switching from Tetrabenazine (Switch): Subjects who are currently receiving an FDA-approved dose of TBZ that is providing a therapeutic benefit for control of chorea associated with HD will be eligible to participate in the study. These subjects will be converted from their TBZ regimen to an SD-809 regimen that is predicted to provide comparable exposure to total (α+β)-HTBZ and (α+β)-HDBZ. Subjects will continue taking their TBZ regimen through midnight at the end of Day 0 and then switch to their assigned SD-809 regimen the next morning. The dose of SD-809 may be adjusted weekly (upward or downward) in increments of 6 mg per day (each week) (6 mg/day or up to 12 mg/day after a total daily dose of 48 mg is reached), until there is adequate control of chorea, the subject experiences a protocol defined "clinically significant" adverse event (defined as related to study medication and either a) is moderate or severe in intensity or b) meets the criteria for a Serious Adverse Event [SAE]), or the maximal allowable dose (72 mg) is reached. If a subject experiences a "clinically significant" AE attributable to SD-809, the Investigator will determine if a dose reduction or suspension is necessary. The Investigator, in consultation with the subject and caregiver, will determine when an adequate level of chorea control has been achieved. Although subjects will enter the long-term treatment period after Week 2, dose adjustment (upward or downward) may continue through Week 4 to optimize dose level. If clinically indicated, additional dose adjustments may be made after Week 4.

Subjects Enrolled from the SD-809-C-15 Study (Rollover): Subjects who have successfully completed Study SD-809-C-15 may be eligible to rollover directly into this study after they complete a 1-week washout period and the Week 13 evaluation of Study SD-809-C-15. To reduce subject burden, the Week 13 evaluation will provide some Baseline data for the present study. Additional evaluations required as part of the SD-809-C-16 study may be completed on the same day as the Week 13 visit of the SD-809-C-15 study after SD-809-C-16 informed consent/assent is obtained. If subjects are unable to enroll at the Week 13 visit they will have up to 3 weeks to complete the additional evaluations for Baseline or the subject will not be eligible to enroll in this study. In addition, following informed consent/assent, prior data from Study SD-809-C-15 can be used in this study as part of the subject's medical history information.

As Rollover subjects will have discontinued study drug (SD-809 or placebo) for at least 1 week at completion of the SD-809-C-15 study, they will undergo titration on SD-809. During titration, the Investigator, in consultation with the subject and caregiver, will determine when an adequate level of chorea control has been achieved. The dose of SD-809 may be adjusted (upward or downward), in increments of 6 mg per day (each week) (6 mg/day or up to 12 mg/day after a total daily dose of 48 mg is reached), until there is adequate control of chorea, the subject experiences a protocol defined "clinically significant" adverse event, as outlined above, or the maximal allowable dose is reached. If a subject experiences a "clinically significant" AE attributable to SD-809, the Investigator will determine if a dose reduction or suspension is necessary. Although subjects will enter the long-term treatment period after Week 2, titration may occur through Week 8 to optimize dose level. Additional dose adjustments may be made after Week 8 if clinically indicated.

Long-Term Treatment Period: During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly. Dose adjustments should be based on all available information including the subject's and caregiver's reports of adverse events and chorea control, information from rating scales, and all safety evaluations. The Long-Term Treatment Period will continue until SD-809 becomes commercially available in the U.S.

Post-Treatment Safety Follow Up: All subjects will discontinue study drug at the End of Treatment visit and return for their final clinic visit one week later for evaluation of safety, cognition, behavior, chorea, and motor function. During this 1-week washout period, subjects should not take prohibited concomitant medications. Subjects will also have a follow-up telephone contact four weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage.

PK Sub-Study (Switch subjects only): A sub-study will be conducted to evaluate the pharmacokinetics (PK) of TBZ and SD-809 in Switch subjects. Approximately 12 subjects will have rich PK sampling and approximately 24 subjects will have sparse PK sampling. The PK of TBZ and metabolites will be assessed at the Baseline visit, and the PK of SD-809 and metabolites will be assessed at the Week 8 visit. If a subject requires a dose change at Week 8, the Week 8 visit assessments should be conducted except for PK sampling, which should be postponed until Week 15.

Table 1 contains the schedule of events for Switch subjects, and Table 2 contains the schedule of events for Rollover subjects.

Table 1: SCHEDULE OF EVENTS A – SUBJECTS *SWITCHING* FROM TETRABENAZINE

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

	Screening			Dose Adjustment		Long Term Treatment								Follow up		Unscheduled	
Study Week→	Up to -4	-1	Baseline [1]	1	2	3	4	7	8	15	28	28 + q13 wks	End of Treatment	1 wk FU	4 wk FU		
Visit Window (days) →		± 3	0	± 1		± 3										n/a	
Visit →	Screening	T1	V1	V2	T2	T3	V3	T4	V4	V5	V6	Vx[17]	End Tx/ET	FU	FFU	UV[18]	UTC
Activity Visit type →	V	TC	V	V	TC	TC	V	TC	V	V	V	V	V	V	TC	V	TC
BARS			X	X			X		X	X	X	X	X	X			
ESS			X	X			X		X	X	X	X	X	X			
Dispense/Order Study Drug[8]		X	X	X	X	X	X		X	X	X	X					X[3]
Drug Acct/Compliance				X			X		X	X	X	X	X				
Assess Adverse Events			X	X	X	X	X		X	X	X	X	X	X	X	X	X
Assess Concomitant Meds	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X
Administer TBZ or SD-809 ER			X[14]						X[15]								
Evaluate Chorea Control (subject/caregiver)	X		X	X	X	X	X		X	X	X	X	X	X		X	X
Return Study Drug													X				

SCHEDULE OF EVENTS KEY SUBJECTS SWITCHING FROM TETRABENAZINE

[V] Clinic Visit

[TC] Telephone Contact

[ET] Early Termination Visit

[FU] Follow Up Visit one week after end of treatment

[FFU] Final Follow Up Visit four weeks after end of treatment

[S] Serum pregnancy test for women of childbearing potential only

[U] Urine pregnancy test for women of childbearing potential only

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

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

1 Baseline visit (Day 0) will occur on the day before the scheduled first dose of SD-809 ER (Day 1)

2 Perform orthostatic blood pressure and pulse after subject is in standing position for at least 3 minutes.

3 Assessments to be completed at Investigator's discretion

4 Brief physical examination, which includes evaluation of the cardiovascular, respiratory, and abdominal systems.

5 Subjects who withdraw early from the study should have a single blood sample collected for PK at the Early Termination Visit if the last dose was within the prior 48 hours, if possible. Subjects who experience an SAE should have a single blood sample collected for metabolites of SD-809 within 48 hours of SAE, if possible

6 Serum follicle stimulating hormone (FSH) level to be assessed in post-menopausal females only (at Screening only).

7 At Screening, administer the C-SSRS Baseline version. At Baseline and every visit thereafter, administer the C-SSRS Since Last Visit version.

8 Study medication supply will be ordered. (See Operations Manual for further details).

9 Provide Diary Card to record meals and tetrabenazine dosing times for upcoming PK sampling day. Subjects should be reminded approx. 7 days before next scheduled visit to complete diary card. Subjects in the "**Rich"** cohort and "**Sparse**" cohort, scheduled for a morning visit, will be reminded to hold dose of tetrabenazine on the day of their Baseline visit. Subjects in the "**Sparse**" cohort, scheduled for an afternoon visit, will be reminded to take their usual dose(s) of tetrabenazine at home per their usual schedule on the day of their Baseline visit.

10 Provide diary card to record the start time of the subject's last meal and the time of their last dose of SD-809 ER prior to the Week 8 visit and ask the subject to bring the diary card with them to the next clinic visit. Subjects should be reminded approx. 7 days before next scheduled visit to complete diary card. Subjects in the "**Rich"** cohort and "**Sparse**" cohort, scheduled for a morning visit, will be reminded to hold dose of SD-809 ER on the day of their Week 8 visit. Subjects in the "**Sparse**" cohort, scheduled for an afternoon visit, will be reminded to take their usual dose(s) of SD-809 ER at home per their usual schedule on the day of their Week 8 visit.

11 Collect and review diary card

12 PK blood sample for tetrabenazine and metabolites

13 PK blood sample for SD-809 and metabolites. If subject requires a dose change at Week 8, PK sampling should be postponed until Week 15.

14 Administer tetrabenazine in clinic if subject scheduled for morning visit. If subject is scheduled for afternoon visit, they will take their usual dose of tetrabenazine at home.

15 Administer SD-809 ER in clinic if subject scheduled for morning visit. If subject is scheduled for afternoon visit, they will take their usual dose of SD-809 ER at home.

16 For subjects on allowed doses of citalopram or escitalopram:

- Week 1: A 12-lead ECG is required at this visit.
- Week 4: If the dose of study drug has been increased since the last ECG, a 12-lead ECG is required at this visit.

17 After Week 28, perform clinic visits every 13 weeks until the End of Treatment Visit. Obtain safety labs and urine pregnancy test every 26 weeks after Week 28, and perform UHDRS-TFC every 52 weeks after Week 28.

18 For subjects requiring an Unscheduled Clinic Visit for any reason, assessments denoted with X should be performed; all other assessments are as indicated at Investigator's discretion (see Section 6.5 of the protocol).

Table 2: SCHEDULE OF EVENTS B – SUBJECTS *ROLLING OVER* FROM SD-809-C-15

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

Dispense/Order Study Drug[6]		X	X	X	X	X	X	X	X	X	X					X[3]
Drug Accountability/Compliance				X		X		X	X	X	X	X				
Assess Adverse Events	*		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Concomitant Meds	*		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluate Chorea Control (subject/caregiver)			X	X	X	X	X	X	X	X	X	X	X		X	X
Return Study Drug												X				

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

[V] Clinic Visit

[TC] Telephone Contact

[ET] Early Termination Visit

[FU] Follow Up Visit one week after end of treatment

[FFU] Final Follow Up Visit four weeks after end of treatment

[U] Urine pregnancy test for women of childbearing potential only

† After Informed Consent is obtained, data from Study SD-809-C-15 will be utilized in this study as part of screening information as detailed in the informed consent/assent.

†† Subjects who have the capacity to provide informed consent only (See Section 6.12 of the protocol)

‡ Data from the Week 13 evaluation of Study SD-809-C-15 will provide some of the Baseline data for the present study, although such data will not become available for this study until informed consent/assent has been provided.

§ May be performed up to 30 days in advance of Baseline

For subjects who were determined to have the capacity to provide informed consent in Study SD-809-C-15.

* Data (Week 12 or earlier) from Study SD-809-C-15 will be utilized in this study as part of screening information.

** Data (Week 13) from Study SD-809-C-15 will be utilized as part of Baseline assessment. Additional specific activities required at this visit are denoted by an "X"

1 Assessment transferred from Screening or Baseline evaluation in Study SD-809-C-15

2 Perform orthostatic blood pressure and pulse after subject is in standing position for at least 3 minutes.

3 Assessments to be completed at Investigator's discretion

4 Brief physical examination, which includes evaluation of the cardiovascular, respiratory, and abdominal systems.

5 The C-SSRS Since Last Visit version is administered at all visits for Rollover subjects

6 Study medication supply will be ordered (See Operations Manual for further details).

7 Subjects who withdraw early from the study should have a single blood sample collected for PK at the Early Termination Visit if the last dose was within the prior 48 hours, if possible. Subjects who experience an SAE should have a single blood sample collected for metabolites of SD-809 within 48 hours of SAE, if possible.

8 For subjects on allowed doses of citalopram or escitalopram:

- Week 2: A 12-lead ECG is required at this visit.
- Week 4: If the dose of study drug has been increased since the last ECG, a 12-lead ECG is required at this visit.

9 After Week 28, perform clinic visits every 13 weeks until the End of Treatment Visit. Obtain safety labs and urine pregnancy test every 26 weeks after Week 28, and perform UHDRS-TFC every 52 weeks after Week 28.

10 For subjects requiring an Unscheduled Clinic Visit for any reason, assessments denoted with X should be performed; all other assessments are as indicated at Investigator's discretion (see Section 6.5 of the protocol).

5 Data Management

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

6 Definition of Population

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

Unless specified otherwise, all data will be summarized for the Safety Population. In addition, two subsets of the Safety Population are defined:

- Rollover Cohort: Successfully completed SD-809-C-15 (First-HD) prior to enrollment into SD-809-C-16 (ARC-HD)
- Switch Cohort: Switched from TBZ to SD-809 for enrollment in SD-809-C-16 (ARC-HD)

7 Endpoints and Rating Scales

7.1 Efficacy Endpoints

The changes from baseline (see sec. 8.7) and from week 8 in total maximal chorea score and total motor score from the UHDRS motor assessment are the efficacy endpoints for this study.

7.2 Safety Endpoints

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

- Incidence of adverse events (AEs), serious AEs (SAEs), severe AEs, drug-related AEs, and AEs leading to withdrawal during the following periods:
  - The entire post-baseline period
  - During the Titration Period (from Day 1 to the end of Week 8) in Rollover subjects
  - During the Dose-Adjustment Period (from Day 1 to the end of Week 4) in Switch subjects
  - During the Extended Dose-Adjustment Period (from Day 1 to the end of Week 8) in Switch subjects who undergo dose adjustment between Weeks 4 and 8 (if at least 10% of Switch subjects have had a dose adjustment between Week 4 and Week 8)
  - During the Stable-Dose Period (Week 8 to end of study)
- Observed values and changes from baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis)
- Observed values and changes from baseline in vital signs
- Observed values in ECG parameters and abnormal findings

- Numbers of subjects with QTcF values > 450 msec, > 480 msec, > 500 msec
- Counts and percentages for Columbia Suicide Severity Rating Scale (C-SSRS)
- Observed values and changes from baseline in the following:
  - Unified Huntington Disease Rating Scale (UHDRS)
  - Unified Parkinson's Disease Rating Scale (UPDRS) (dysarthria)
  - Barnes Akathisia Rating Scale (BARS)
  - Hospital Anxiety and Depression Scale (HADS)
  - Epworth Sleepiness Scale (ESS)
  - Montreal Cognitive Assessment (MoCA©)
  - Swallowing Disturbance Questionnaire (SDQ)
- Duration of time to achieve a stable dose of SD-809, defined as the number of days from Day 1 until the first day at which the subject was taking the dose level they were receiving at Week 8.

7.3 Rating Scales

7.3.1 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. 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.

7.3.2 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an FDA endorsed questionnaire to screen for suicidality in trials of central nervous system active compounds. The C-SSRS is an interview by trained study personnel that should be done at Screening, Baseline (Day 0), and during the study as outlined in the Schedule of Events. The form provided at Screening collects the history of suicide using a C-SSRS form version termed "Baseline", and subsequent visits use a C-SSRS form version termed "Since the Last Visit."

7.3.3 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. The components of the UHDRS are:

- Motor Assessment, which includes the total maximal chorea (TMC) score and the parkinsonism subscale score (sum of finger taps, pronate/supinate - hands, rigidity - arms, bradykinesia - body, gait, tandem walking, and retropulsion pull test scores)
- Cognitive Assessment
- Behavioral Assessment
- Independence Scale

- Functional Assessment
- Total Functional Capacity (TFC)
- Clinical Summary

7.3.4 Montreal Cognitive Assessment (MoCA©)

The 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. 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.

7.3.5 Unified Parkinson Disease Rating Scale (UPDRS)

The 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 speech/dysarthria will be utilized to screen and monitor study subjects for parkinsonism.

7.3.6 Barnes Akathisia Rating Scale (BARS)

The 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.

7.3.7 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire, composed of eight questions, that provides a measure of a subject's general level of daytime sleepiness. 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 higher scores indicating a higher level of daytime sleepiness.

7.3.8 Swallowing Disturbance Questionnaire (SDQ)

The SDQ is a self-administered questionnaire comprising 15 questions that assess the frequency of swallowing disturbance. Scores range from 0.5 (normal) to 44.5 (severe impairment).

8 Statistical Methods

8.1 Hypothesis Testing

Because this is an open-label, single-arm trial, no formal statistical analyses will be conducted.

8.2 Sample Size

This is an open-label, single-arm safety study, and the sample size is not based on statistical considerations.

8.3 Subject Withdrawal

Subjects may withdraw from the study at any time. Subjects may be withdrawn from study treatment or the study at the request of the Investigator or Sponsor.

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

8.4 Final Analyses and Reporting

For Rollover subjects from the First-HD study, the subject's prior treatment assignment (SD-809 or placebo) will remain blinded until that study's final database has been locked and unblinded.

The final databases for this study may not be locked until this SAP has been approved. The analyses outlined in this SAP will be carried out after:

- The SAP has been approved;
- The corresponding study database has been authorized by the sponsor clinical team as complete and finalized.

Further exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be clearly identified in the CSR.

8.5 Handling of Missing Data

8.5.1 Missing Data for Individual Items of an Instrument

For the Total Motor Score and the TMC Score of the UHDRS, missing data items will be imputed, provided that at least 80% of the items for the corresponding score are nonmissing. In such cases, the value(s) of the missing item(s) will be imputed by carrying forward the most recent nonmissing value of the corresponding item. However, if more than 20% of the items for the score are missing, the score will be treated as missing.

For all other missing data items, the missing data items will remain missing and will not be imputed, and only observed data will be summarized.

8.5.2 Missing Endpoint Data

Missing endpoint data will not be imputed, and only observed data will be summarized.

8.6 Interim Analysis

An interim analysis of the safety and open-label efficacy data was conducted to assess the adequacy of the dose conversion strategy and the activity of SD-809 in treating chorea. Details can be found in Appendix 1.

8.7 Comments on Statistical Analysis

The following general comments apply to all statistical analyses and data presentations:

- Unless otherwise specified, all data will be summarized separately for the Rollover Cohort and the Switch Cohort.
- Summaries will include frequencies and percentages for categorical data and the number of observations, mean, standard deviation, median, minimum, and maximum for continuous data.
- Duration variables will be calculated using the general formula: (end date – start date) + 1.
- Unless specified otherwise, for subjects in the Switch cohort, the baseline value is the last available value prior to the first administration of SD-809 on Day 1. For Rollover subjects from the First-HD study, for assessments that were scheduled to be performed at Week 13 of that study or the Baseline visit of the ARC-HD study, the baseline value is the last available off-treatment (at least 4 days after the last administration of study drug) value prior to administration of SD-809 on Day 1. For assessments that were not scheduled to be performed at Week 13 of the First-HD study or at the Baseline visit of the ARC-HD study, the baseline value is the last available value prior to administration of study drug on Day 1 of the First-HD study. For the Switch cohort, the baseline value used for calculating change from baseline for TMC and the total motor score will be the mean of the values from the Screening and Baseline visits.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numeric type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower or upper limit of normal range such as '<10' or '<5' will be treated as '10' or '5', respectively, and a value such as '>100' will be treated as '100.' However, the actual values as reported in the database will be presented in data listings.
- Individual subject listings of all data represented on the eCRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all data.
- Version 9.4 of SAS statistical software package will be used to provide all summaries, listings, and graphs described in this document.

- All raw data will be presented to the original number of decimal places. Means and medians will be presented to one more decimal place than the raw data. Standard deviations will be presented to two more decimal places than the raw data.

- The denominator for percentages will be based on the number of subjects or observations with non-missing data appropriate for summary purposes. Unless otherwise noted, all percentages will be presented to one decimal place.

8.8 Time Periods for Analyses

Some analyses will be performed by time period. For these analyses, the following definitions will be used:

- Screening Period (Switch subjects only) - from informed consent until the first dose of study drug

- Dose-Adjustment Period (Switch subjects only) – Baseline through Week 4

- Extended Dose-Adjustment Period (Switch subjects only) – Baseline through Week 8

- Titration Period (Rollover subjects only) – Baseline through Week 8

- Stable-Dose Period - from Week 8 through the last dose of study drug

- Entire Treatment Period - Baseline through last dose of study drug

- Follow-up Period - from the last dose of study drug through the end of the study

Subjects who withdraw from the study during the Titration Period or the Extended Dose-Adjustment Period will not have a Stable-Dose Period. For the analyses of adverse events, to be conservative, all follow-up adverse events will be counted as events that occurred during the last available treatment period prior to the Follow-up period.

8.9 Analysis Visit Windows

For efficacy and safety by-visit analyses, data collected at post baseline scheduled visits will be included using their nominal visit. Data collected at early termination, end of treatment, and unscheduled visits will be assigned to a visit window as described below. All scheduled visits will be assigned a target study day; for the determination of target days, weeks will be assumed to have 7 days. Thus, Week 4 would have a target day of 4*7=28 days. For each visit, a visit window will be assigned so that anything from the midpoint to the prior target day to the midpoint to the following target day will be assigned to that visit window as shown in Table 3 below. The following rules concerning visit windows and selecting records for analysis will be used:

1. Scheduled visit has precedence.

2. If there are multiple records of the same scheduled visit, the record closest to the target day will be used for analysis. If two records are equidistant, then the earlier one will be used.

3. For a given visit, if there is no data from a scheduled visit, data from an unscheduled visit that occurs in the visit window will be used for analysis.

Table 3: Analysis Visit Window

Visit	Target Day	Visit Window
Screening	-5	(--, -5)
Screening Telephone Contact	-2	(-4, -2)
Baseline	-1	(-1, -1)
Week 1	7	(1,10)
Week 2	14	(11-17)
Week 3	21	(18, 24)
Week 4	28	(25, 31)
Week 5	35	(32, 38)
Week 7	49	(39, 52)
Week 8	56	(53, 80)
Week 15	105	(81, 150)
Week 28	196	(151, 241)
Week 41	287	(242, 332)
Week 54	378	(333, 423)
Week 67	469	(424, 514)
Week 80	560	(515, 605)
Week 93	651	(606, 697)
Week 106	742	(698, 787)
Week 119	833	(788, 879)
Week 132	924	(880, 970)
Week 145	1015	(971, 1060)
Week 158	1106	(1061, 1152)
Week 171	1197	(1153, --)

8.10 Changes to Protocol-Specified Analyses

The protocol stated that a subject would be deemed compliant if the subject has taken 80% to 100% of the expected tablets; however, this was changed, and a subject will be deemed to be compliant if the subject has taken 80% to 105% of the expected tablets.

TMC and the total motor score from the UHDRS were listed as safety parameters in the protocol; however, these parameters were changed to efficacy endpoints for this SAP.

9 Statistical Analyses

9.1 Subject Disposition

The number and percent of enrolled subjects who were screen failures, who were included in the Safety Population, who completed the study, and who withdrew from the study, and their primary reason for withdrawal, will be summarized. Subject disposition will be summarized using all enrolled subjects. Enrolled subjects are those subjects who signed the informed consent form.

For screen failures, the reason that subjects were declined and the reason that subjects were excluded from the study will be summarized using counts and percentages.

A listing summarizing whether subjects completed or discontinued from the study will also be presented, and the primary reason for discontinuation will be provided for those subjects who withdrew.

9.2 Demographic and Baseline Characteristics

Descriptive statistics or counts and percentages, as appropriate, will be used to summarize demographic and baseline characteristics in the Safety Population. Subject demographics include age, gender, race, ethnicity, education (years), CAG repeat length, height, weight, and body mass index (BMI) at screening, whether or not the subject was a CYP2D6 poor metabolizer, and disease duration (in years). Age (in years) will be calculated from the date of birth to the date of informed consent in Protocol SD-809-C-16 for both Switch and Rollover subjects. Age will be reported as an integer. BMI will be calculated using the following formula: BMI (kg/m^2) = weight (kg)/(height (m))^2. Only the year of diagnosis is collected in the CRF, so disease duration (years) will be calculated using the following formula: (Date of Informed Consent - July 1 of Year of Diagnosis)/365.25.

All demographic and baseline characteristics will also be listed.

9.3 Medical History

Medical history will be obtained at Screening for C-16 Switch subjects and recorded in the eCRF and transferred from data collected in C-15 for Rollover subjects.

Medical history information will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) high level group term and preferred term using counts and percentages. Medical history information will also be listed.

9.4 Concomitant Medications

Concomitant medications are defined as medications taken any time after the start of dosing until the final visit. Medications are also considered concomitant if their stop date is unknown or marked as continuing. Medications with missing start dates will be considered ongoing on the first day of study drug administration, except where positive confirmation is available that the medication was stopped before study drug administration.

The World Health Organization Drug Dictionary (WHODRUG) will be used to classify prior and concomitant medications by therapeutic class and preferred term. The WHODRUG version will be noted in the CSR. The number and percentage of subjects receiving concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 and preferred term. Subjects will be counted only once for an ATC class, even if the subject took the same medication on multiple occasions or more than one medication in the same ATC class. Similarly, subjects will be counted at most once for a preferred term, even if they took the same medication on multiple occasions or more than one medication with the same preferred term. The number and percentage of subjects receiving concomitant medications at baseline will also be summarized by ATC level 3 and preferred term.

A listing of concomitant medications will also be presented.

9.5 Study Drug Exposure and Compliance

The Investigator or designated study staff is responsible for monitoring the subject's compliance with study drug during the trial. Compliance will be assessed by tablet count obtained from returned study drug containers and must be reviewed at every visit while the subject is still in the clinic to determine if the subject is taking study drug as directed.

Percent compliance in the interval between visits will be calculated as $100 \cdot$(number of tablets used/number of tablets expected to be used), where number of tablets used = number of tablets dispensed minus number of tablets returned. A subject will be deemed compliant if the subject has taken 80% to 105% of the expected number of tablets of study drug; this definition of compliance supersedes the definition specified in the study protocol.

For Switch subjects, percent compliance will be summarized for the following time periods using descriptive statistics: from Day 1 to the Week 4 visit, from Day 1 to the Week 8 visit, and from Day 1 to the last dose of study drug. For Rollover subjects, percent compliance will be summarized for the following time periods using descriptive statistics: from the Day 1 to the Week 8 visit and from Day 1 to the last dose of study drug. Compliance will be summarized for these same time periods using counts and percentages.

The length of time (in days) that each subject is exposed to SD-809 will be summarized using descriptive statistics. For subjects who complete the study through Week 8, the duration of time in days from Day 1 until the day of first receiving the SD-809 dose received at Week 8 (i.e., the duration of time to achieve a stable dose of SD-809) will be summarized using descriptive

statistics. For Switch subjects who complete the study through Week 8, the number and percentage of subjects who achieve a stable dose by Week 4 (i.e., received the same dose of SD-809 at Week 4 that they received at Week 8) will be presented.

For each subject, the initial dose, titrations, and investigator-initiated dose changes that occur during the study will be listed.

9.6 Protocol Deviations

Deviations from the protocol will be recorded appropriately. Protocol deviations will include the following:

- Subjects who did not give appropriate Informed Consent
- Subjects enrolled who did not meet the inclusion/exclusion criteria
- Subjects who took disallowed or prohibited medications
- Subjects who were not 80% - 105% treatment compliant
- Key endpoint non-compliance: TMC, UHDRS Behavior, HADS, C-SSRS, UPDRS, SDQ, BARS or ESS not performed for 2 or more consecutive expected visits
- Subjects who were administered the wrong study treatment
- Subjects who were administered an incorrect dose or an incorrect starting dose for switch cohort subjects (a dose adjustment would not be considered an incorrect dose)
- Missing safety endpoints at any visit: SDQ, BARS, HADS, or C-SSRS
- Missing lab tests, PK sampling, vital sign and ECG at any visit
- Out of protocol-specified window visits

A listing of protocol deviations will be provided.

9.7 Efficacy Analyses

For TMC and the total motor score of the UHDRS, the Rollover and Switch cohorts will be analyzed separately through Week 8. Descriptive statistics will be presented by visit for the actual data and for the changes from baseline, including 95% confidence intervals for the true mean changes from baseline. For the Switch cohort, the baseline value used for calculating change from baseline for TMC and the total motor score will be the mean of the values from the Screening and Baseline visits. These analyses will be repeated for TMC using data at scheduled visits only and also only using subjects with a TMC score at all scheduled visits up to Week 15.

In addition, for TMC and the total motor score, descriptive statistics will be presented by visit for the actual data and the changes from Week 8, including 95% confidence intervals for the true mean changes from Week 8. Subjects without a Week 8 assessment will be excluded from the analysis. This analysis will be done for the prior SD-809 subjects in the rollover cohort, prior placebo subjects in the rollover cohort, the switch cohort, and the two cohorts combined.

9.8 Analysis of Dose Level

Total daily dose level (mg) at Week 1 (Switch cohort)/Week 2 (Rollover cohort), and each scheduled visit will be summarized for each cohort using descriptive statistics. The baseline tetrabenazine dose level will be summarized for the Switch cohort. In addition, the number and percentage of subjects at each dose level will be summarized for each visit.

The total daily dose level will also be summarized by visit using descriptive statistics for the subjects with a corresponding TMC score at the given visit.

9.9 Safety Analyses

Safety will be assessed using the Safety Population.

9.9.1 Adverse Events

Adverse events will be coded using version 16.1 of the Medical Dictionary for Regulatory Activities (MedDRA); the MedDRA version will be noted in the CSR. Treatment-emergent AEs (TEAEs) are events that 1) begin after treatment with study drug in the current study and that are not present at baseline or 2) if present at baseline, have worsened in severity. For AEs with missing start dates, the AE will be considered treatment-emergent unless there is additional information indicating that the AE started prior to the first treatment. All analyses of TEAEs will be performed separately for TEAEs that occurred during the titration period (for Rollover subjects only), during the dose-adjustment period (for Switch subjects only), during the extended dose-adjustment period (for Switch subjects only), during the stable dose period, and during the entire treatment period. To be conservative, all adverse events that occurred during the follow-up period will be counted as events that occurred during the last available treatment period. In order to be included in the analysis for a given time period, a subjects must have at least one visit during the time period.

For the Switch cohort, an overview of AEs occurring during the Screening period will present the number and percentage of subjects in the following categories:

- Any AEs
- Any serious AEs (SAEs)
- Any severe AEs
- Any AE(s) leading to death

An overview of TEAEs will present the number and percentage of subjects in the following categories:

- Any TEAEs
- Any serious TEAEs

- Any severe TEAEs
- Any treatment-related TEAEs
- Any TEAEs resulting in dose reduction
- Any TEAEs resulting in dose suspension
- Any TEAEs resulting in withdrawal from the study
- Any treatment-related TEAEs resulting in withdrawal from the study
- Any TEAEs resulting in dose reduction, dose suspension, or withdrawal from the study
- Any TEAE(s) leading to death

TEAEs, serious TEAEs, TEAEs that led to dose reduction, TEAEs that led to dose suspension, TEAEs that led to withdrawal from the study, TEAEs that occurred in at least 4% of Rollover or Switch cohort subjects in the Safety Population across all time periods,will be summarized at the subject level by MedDRA system organ class (SOC) and preferred term using frequencies and percentages.

Exposure adjusted incidence rates (number of patients with an event per person-year) will also be presented for the above TEAE overview categories, all preferred terms, and selected AEs of interest by patient cohort and study (First Active in C15, First Placebo in C15, Rollover in C16, and Switch in C16). AEs of agitation, somnolence, insomnia, anxiety and fall will be defined as events with matched preferred terms. In addition, AEs with selected preferred terms will be combined into the AEs of interest as follows:

- Akathisia and Restlessness: Akathisia, Hyperkinesia, Psychomotor hyperactivity, Restlessness, Agitation
- Dysphagia: Aphagia, Dysphagia
- Parkinsonism: Akinesia, Bradykinesia, Cogwheel rigidity, Freezing phenomenon, Hypertonia, Masked facies, Muscle rigidity, On and off phenomenon', Parkinsonian crisis, Parkinsonian gait, Parkinsonian rest tremor, Parkinsonism, Parkinson's disease, Resting tremor
- Suicidality: Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Poisoning deliberate, Self-injurious ideation, Suicidal behavior, Suicidal ideation, Suicide attempt.
- Depression: all preferred terms containing “depression”

Incidence rate will be calculated as:

Number of patients with given event/ Person-years for the event

Person-years for a selected event are defined as the sum of exposure days across all subjects divided by 365.25. Subjects with an event of the given type contribute days from the date of their first treatment dose until the date of the first event of the given type. Subjects without an event of the given type contribute days from date of their first treatment dose until their treatment end date. Events that occurred after the last dose date of each study period were not included.

TEAEs and treatment-related TEAEs, categorized by system organ class, preferred term, and maximum severity (mild, moderate, or severe), will be summarized by study period using counts and percentages. In addition, TEAEs, categorized by system organ class, preferred term, and relationship to study drug (unrelated, related), will be summarized by study period using counts and percentages. TEAEs that are classified as possibly, probably, or definitely related to study drug on the AE eCRF, or for which the relationship to study drug is missing, will be considered treatment related. Unrelated AEs include those classified as unrelated or unlikely related on the AE eCRF.

Subjects receiving a strong CYP2D6 inhibitor or who are poor CYP2D6 metabolizers are considered to have impaired CYP2D6 function. The following AE analyses will be repeated by impaired CYP2D6 function category at baseline (subjects receiving a strong CYP2D6 inhibitor at Baseline, subjects not receiving a strong CYP2D6 inhibitor at Baseline, CYP2D6 poor metabolizers, non-CYP2D6 poor metabolizers, subjects with impaired CYP2D6 function, and subjects without impaired CYP2D6 function):

- Overview of TEAEs
- TEAEs by SOC and preferred term

For TEAE summaries, if a subject has more than one TEAE within a preferred term, the subject is counted once in that preferred term at the maximum severity and at the closest relationship to study drug. If a subject has more than one TEAE within a system organ class, the subject is similarly counted once in that system organ class.

Complete listings of all AEs will be provided. In addition, data listings of all SAEs, AEs leading to withdrawal from the study, and AEs leading to death will also be provided.

9.9.2 Vital Signs and Weight

Respiration rate (breaths/minute), temperature (°C), and weight (kg) will be obtained at each clinic visit. Supine and standing systolic and diastolic blood pressure (mmHg) and supine and standing heart rate (beats/minute) will be collected at the Baseline, Week 8, and End-of-Treatment/Early Termination visits. Seated blood pressure and heart rate will be collected at all other visits.

Weight, respiration rate, temperature, seated/supine systolic and diastolic blood pressure, and seated/supine heart rate, and the corresponding change from baseline, will each be summarized by visit using descriptive statistics.

A listing of weight and vital sign assessments will also be provided.

9.9.3 Orthostatic Vital Signs

Orthostatic blood pressure and heart rate will be recorded at Baseline and Week 8. The Baseline and Week 8 differences between supine and standing systolic and diastolic blood pressure and heart rate, and the change from Baseline to Week 8 in these differences will be summarized using descriptive statistics.

9.9.4 Physical and Neurological Examinations

Physical examination findings will be listed.

A complete neurological examination will include evaluation of the following categories:

- Cranial nerves
- Motor system (muscle strength, coordination)
- Sensory (sensation)
- Reflexes (muscle strength reflexes, plantar response)

Neurological examination findings will be listed.

9.9.5 Electrocardiogram (ECG)

A safety electrocardiogram (ECG) will be recorded at Screening and the Week 8 visit for all subjects. For subjects on allowed doses of citalopram or escitalopram, additional ECGs will be performed at Week 1 (Switch subjects) or Week 2 (Rollover subjects) and at Week 4 if the dose of study drug has been increased since the last ECG.

A cardiologist will provide a clinical interpretation of each ECG that will be recorded in the eCRF. ECG parameters that will be recorded include heart rate, PR interval, QRS duration, QT interval, and QTcF (QT interval corrected for heart rate using Fridericia's formula).

Descriptive statistics will be used to summarize ECG parameters at Screening and the Week 8 visit. Descriptive statistics will also be used to summarize QTcF values at Screening and the Week 8 visit for subjects with a QTcF value >450 msec at any visit. These analyses will be repeated for the Screening, Week 1 (Switch subjects) or Week 2 (Rollover subjects), Week 4, and Week 8 visits for subjects receiving allowed doses of citalopram or escitalopram at Baseline.

The number and percentage of subjects with normal, abnormal not clinically significant, abnormal clinically significant, and abnormal with clinical significance not specified ECGs will be summarized at Screening and the Week 8 visit. The number and percentage of subjects with PR >200 msec, QRS >100 msec, QT >500 msec, QTcF >450 msec, QTcF >480 msec, and QTcF >500 msec, will be similarly summarized. These analyses will be repeated for the Screening, Week 1 (Switch subjects) or Week 2 (Rollover subjects), Week 4, and Week 8 visits for subjects receiving allowed doses of citalopram or escitalopram at Baseline.

ECG results will also be listed.

9.9.6 Clinical Laboratory Assessments

Serum chemistry, hematology, and urinalysis laboratory tests will be performed at Screening (Switch subjects only), Baseline (Switch subjects only), Week 8, Week 28, Week 41, Week 54, and every 26 weeks thereafter. For Rollover subjects, the screening assessment will be prior data from study SD-809-C-15. Laboratory parameters that will be assessed include the following:

Table 4: Clinical Laboratory Tests

Serum Chemistry		
• Sodium	• Creatinine	• Albumin
• Potassium	• Total calcium	• Total bilirubin
• Chloride	• Phosphate	• Direct bilirubin
• Bicarbonate	• Uric Acid	• Alkaline phosphatase (ALP)
• Magnesium	• Cholesterol	• Alanine aminotransferase (ALT)
• Glucose	• Triglycerides	• Aspartate transaminase (AST)
• Blood urea nitrogen (BUN)	• Total Protein	• Lactate dehydrogenase (LDH)

Hematology	*Urinalysis*
• Hemoglobin	• Leucocytes
• Hematocrit	• Nitrites
• Red blood cell count (RBC)	• Urobilinogen
• Mean cell volume (MCV)	• Protein
• Platelets	• pH
• White cell count	• Blood
• Neutrophils	• Specific gravity
• Lymphocytes	• Ketone
• Monocytes	• Bilirubin
• Eosinophils	• Glucose
• Basophils	• Microscopic exam (if indicated)

Screening Labs	*Other*
• Urine and serum pregnancy tests (women of childbearing potential only) • Follicle Stimulating Hormone (FSH) for post-menopausal women only. • Hepatitis B surface antigen (HBsAg)	• CYP2D6 genotype (blinded) • CAG repeat • Prothrombin Time

Serum chemistry and hematology results and changes from screening/baseline will be summarized at each visit using descriptive statistics. In addition, all serum chemistry and hematology results will be categorized into the following categories using the laboratory reference ranges: below lower limit of normal, normal, above upper limit of normal. Shift tables summarizing changes in status from screening/baseline to each post-baseline visit will be presented. All laboratory results including urinalysis results will be listed.

9.9.7 Other Safety Assessments

Other safety outcomes include the following:

- HADS (HADS Anxiety subscale [HADS-A] score and HADS Depression subscale [HADS-D] score)
- C-SSRS

- MoCA© (total score)
- UHDRS
    - Parkinsonism subscore
    - Verbal fluency test score,
    - Symbol digit modalities test score
    - Stroop interference test scores of the cognitive exam, including raw color naming score, raw word reading score, raw interference score, as well as the adjusted interference score[1]. The adjusted interference score can be calculated by subtracting a "predicted score", calculated as (raw color naming *raw word reading)/(raw color naming + raw word reading), from the raw interference score.
    - Behavioral assessment item scores (the product of frequency and severity) (depressed mood, apathy, low self-esteem/guilt, suicidal thoughts, anxiety, irritable behavior, disruptive or aggressive behavior, perseverative/obsessional thinking, compulsive behavior, delusions, hallucinations), behavioral assessment total score (sum of frequency × severity item scores)
    - Functional assessment score
    - Independence scale score
    - Total functional capacity (TFC) score
    - Question 78 and 79 scores of the clinical summary section (Part VII)]
- UPDRS dysarthria (speech score)
- SDQ (total score)
- BARS (summary score and global clinical assessment of akathisia score)
- ESS (total score)
- Duration of time to achieve a stable dose of SD-809

For all quantitative data (which includes all of these assessments except for the C-SSRS and the Question 78 and 79 scores of the UHDRS), except the duration of time to achieve a stable dose of SD-809, descriptive statistics will be presented by visit for the actual data and for the changes from baseline. For the ESS total score, SDQ, UPDRS (speech) and the BARS scores, 95% confidence intervals will be presented for the true mean changes from baseline. Descriptive statistics (and 95% confidence intervals for the true mean changes from Week 8 for the ESS total

score, SDQ, UPDRS (speech) and the BARS scores) will also be presented by visit for the actual data and for the changes from Week 8 for the UHDRS parkinsonism subscore, the UHDRS cognitive exam scores, the behavioral assessment item scores and total score, the SDQ total score, the UPDRS dysarthria speech score, the HADS scores, the BARS scores, the ESS total score, and the MoCA© total score. Analyses of the UHDRS cognitive exam scores will be repeated excluding sites with conflict of interest or good clinical practice violations. Results of Questions 78 and 79 from the Clinical Summary section (Part VII) of the UHDRS will be summarized by visit using counts and percentages.

For C-SSRS, the number and percentage of subjects with suicidal ideation at any post-baseline time point (overall and by individual question), suicidal behavior at any post-baseline time point (overall and by individual question), suicidal ideation or behavior at any post-baseline time point (overall and by individual question), and self-injurious behavior without suicidal intent at any post-baseline time point will be presented for each treatment group. The number and percentage of subjects with suicidal ideation [affirmative ("YES") answer to questions 1 or 2 at any post-baseline time point], with suicidal behavior [affirmative ("YES") answer to questions 6, 7, 8 or 9 at any post-baseline time points], and who completed suicide [affirmative ("YES") answer to question 10 at any post-baseline time point] post-baseline will also be presented.

9.10 Pharmacokinetic Assessments

Blood samples will be obtained for measurement of plasma concentrations of alpha (α)-HTBZ, beta-(β)-HTBZ, total (α+β)-HTBZ, alpha (α)-HDBZ, beta-(β)-HDBZ, total (α+β)-HDBZ, and other metabolites, as required in subjects switching from TBZ to SD-809.

Plasma concentrations will be listed at each measured time point. Plasma concentrations will be used in a separate population PK analysis.

10 References

[1] The Stroop Color and Word Test Manual. 1998, 2002. Stoelting Co., Wood Dale, IL.

APPENDIX 1: **Interim Analysis**