Statistical Analysis Plan

An Open-Label, Long-Term Safety Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia

Study Number SD-809-C-20

NCT02198794

SAP Approval Date: 03 December 2019

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Phase 3

EudraCT number: 2014-001891-73

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Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: An Open-Label, Long-Term Safety Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia

Study Title: SD-809-C-20

Statistical Analysis Plan for:

☐ Interim Analysis ☐ Integrated Summary of Efficacy

☒ Final Analysis ☐ Integrated Summary of Safety

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Approver: [redacted] Date
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	analysis of covariance
BARS	Barnes Akathisia Rating Scale
BMI	Body Mass Index
C-SSRS	Columbia-Suicide Severity Rating Scale
CGIC	Clinical Global Impression of Change
CRF	case report form
CSR	clinical study report
DRA	dopamine receptor antagonist
EAIR	Exposure-Adjusted Incidence Rate
ECG	Electrocardiogram
EOT	end of treatment
ESS	Epworth Sleepiness Scale
ET	early termination
HADS	Hospital Anxiety and Depression Scale
ITT	intent-to-treat
mCDQ-24	Modified Craniocervical Dystonia Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MoCA©	Montreal Cognitive Assessment
NDA	new drug application
PGIC	Patient Global Impression of Change
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standard MedDRA Queries
TD	tardive dyskinesia
UPDRS	Unified Parkinson's Disease Rating Scale
WHO drug	World Health Organization Dictionary of Medical Codes

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. study SD-809-C-20 (An Open-Label, Long-Term Safety Study of SD-809 [Deutetrabenazine] for the Treatment of Moderate to Severe Tardive Dyskinesia), and was written in accordance with SOP GBP_RD_702 (Statistical Analysis Plan).

The reader of this SAP is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (eg other endpoints).When differences exist in descriptions or explanations provided in the study protocol and this SAP, the SAP prevails; the differences will be explained in the Clinical Study Report.

1. STUDY OBJECTIVES

The objectives of this study are:

- Evaluate the safety and tolerability of long-term maintenance therapy with SD-809
- Evaluate the efficacy of long-term maintenance therapy of SD-809 to reduce the severity of abnormal involuntary movements of tardive dyskinesia (TD)
- Evaluate the persistence of the therapeutic effect of SD-809

2. STUDY DESIGN

2.1. General Design

This is an open-label, single-arm study in which patients with moderate to severe drug-induced TD who have successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of SD-809 for the treatment of moderate to severe TD) will be invited to participate.

Patients who have successfully completed a parent study may be eligible to rollover directly into this study after they complete a 1-week washout period and the Week 13 evaluation of the parent study. To reduce patient burden, after obtaining informed consent/assent, some data collected in the parent study will be used in the SD-809-C-20 study and will provide some of the baseline data for SD-809-C-20 (see Table 1). In addition to assessments completed for the parent study Week 13 visit, evaluations required as part of the SD-809-C-20 study will be completed on the same day as the Week 13 visit.

Part A:

Titration Period (up to 6 weeks): As all patients will have discontinued study drug (SD-809 or placebo) for 1 week at completion of the parent study, they will undergo titration on SD-809 in this study. During titration, the Investigator, in consultation with the patient (and caregiver, if appropriate), will determine when an adequate level of dyskinesia control has been achieved. The dose of SD-809 should be adjusted (upward or downward) once per week, in increments of 6 mg per day, until there is adequate control of dyskinesia, the patient experiences a protocol-defined clinically significant adverse event (defined as related to study drug and either a) moderate or severe in intensity or b) meeting the criteria for an SAE), or the maximal allowable dose is reached. If a patient experiences a clinically significant AE attributable to SD-809, the Investigator will determine if a dose reduction, dose suspension, or withdrawal from the study is necessary. Patients will have a telephone contact at Week 1 and a clinic visit at Week 2, to evaluate safety and establish a dose of study drug that adequately controls dyskinesia and is well tolerated. ***Although patients will enter the long-term treatment period after Week 2, titration to optimize dose should occur through Week 6.***

Long-Term Treatment Period (Week 3 until the last dose in Part A): During the Long-Term Treatment Period, patients will continue titration through Week 6. During titration, all patients will be contacted by telephone at Week 3 (the first week of the Long-Term Treatment Period) and Week 5 and will return to the clinic at Week 4 and Week 6 for evaluation of safety and dyskinesia control. Patients who have not achieved a stable dose by the Week 6 visit may have unscheduled visits or telephone contacts to further adjust their dose upward or downward. Site interactions for dose adjustment should alternate between telephone contacts and clinic visits. During the remainder of the Long-Term Treatment Period, patients will return to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at the last dose in Part A (completion of Part A=Week 158 or beginning of Part B after Amendment 06 implementation). During long-term treatment, further dose adjustments of SD-809 may be made, if necessary, but not more often than weekly and in increments of 6 mg per day. In the case of the addition of a strong CYP2D6 inhibitor (i.e., paroxetine, fluoxetine, and bupropion), a greater

dose reduction may be required. Dose reductions in this context should be reviewed with the Medical Monitor. Dose adjustments should be based on all available information, including the patient's and caregiver's reports of adverse events and dyskinesia control, information from rating scales, and all safety evaluations. If warranted, study sites are encouraged to conduct periodic phone calls with the patients to ensure adherence to the treatment regimen and retention of unused drug containers.

Patients who have been on a stable dose of SD-809 and any concomitant dopamine receptor antagonists (DRA) for a minimum of 4 weeks will be invited to participate in the Randomized Withdrawal Period (Part B) at the next routine visit at the site after approvals from IRB/Ethics Committee and as required by country regulations. If the patient chooses to participate in Part B, then participation in Part A will end. Patients who decline to participate in Part B will continue in Part A until Week 158. Patients who decline participation in Part B will be given an ongoing option to participate at subsequent study visits.

Part B:

Part B will consist of a double-blind; Randomized Withdrawal Period; treatment with SD-809; and post-treatment safety follow-up. The Randomized Withdrawal Period will be 1 week (+3 days maximum) in duration and will consist of 2 visits, the Pre-Withdrawal Visit and the Post-Withdrawal Visit. After the Randomized Withdrawal Period, the patients will resume treatment with SD-809 on the prior established dose for an additional 12 weeks until end of treatment (EOT). A follow-up telephone call will occur 4 weeks after EOT.

At the beginning of the Randomized Withdrawal Period, patients will be randomized in a blinded fashion to either SD-809 (current dose) or placebo in a 1:1 ratio stratified by concomitant DRA usage. Up to 194 patients (active patients as of the approval date of Amendment 06) will be randomized (SD-809 or placebo). Patients will be required to sign a written informed consent.

Patients will need to be on a stable dose of SD-809 and any concomitant DRA for a minimum of 4 weeks before starting the Randomized Withdrawal Period.

Patients will be scheduled to return 1 week (+3 days maximum) after the Pre-Withdrawal Visit of the Randomized Withdrawal Period for efficacy and safety assessments.

At the end of this period, patients will continue treatment with SD-809 at the previous dose administered before the Randomized Withdrawal Period (last dose in Part A). Treatment with SD-809 will continue for 12 weeks until the EOT visit.

Video ratings of the AIMS will occur at the Pre-Withdrawal Visit, the Post-Withdrawal Visit, and the EOT/early termination (ET) visit.

Post-Treatment Safety Follow-up:

Part A:

Patients who do not participate in Part B will continue in Part A, discontinue study drug at the Week 158 visit, and return for their final clinic visit at Week 159 for evaluation of safety, dyskinesia control, and motor function. During this 1-week follow-up period, patients should continue to not take prohibited concomitant medications. Patients will also have a follow-up telephone contact at Week 162, 4 weeks after their last dose of study drug, to evaluate adverse events and concomitant medication usage.

Patients who discontinue study drug in Part A will complete an ET visit; a follow-up clinic visit 1 week later to evaluate safety, dyskinesia, and motor function; and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.

Part B:

Patients who complete the Randomized Withdrawal Period and subsequent 12 weeks of treatment will complete an EOT visit and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since EOT.

Patients who discontinue study drug in Part B will complete an ET visit; a follow-up clinic visit 1 week later to evaluate safety, dyskinesia, and motor function; and a follow-up telephone contact 4 weeks after the last dose of study drug to evaluate the adverse events and concomitant medication use since ET.

Schedule of events are outlined in Table 1.

Table 1: Schedule of Events

Part A

	Screening		Year 1										Year 2				Year 3				Follow-up clinic visit	Follow-up call	Unscheduled	
			Titration Period		Long-Term Treatment Period																			
Study Week[l] →	**Prior Data from Parent Study†**	**Base-line‡**	**1**	**2**	**3**	**4**	**5**	**6**	**15**	**28**	**41**	**54**	**67**	**80**	**93**	**106**	**119**	**132**	**145**	**158[10]/ET[11]**	**159 or 1 week after ET**	**162 or 4 weeks after ET**		
Visit Window (days)		+3	± 1														± 3							
Activity Visit Type →		V	TC	V	TC	V	TC	V	V	V	V	V	V	V	V	V	V	V	V	V	V	TC	V	TC
Evaluate/Adjust Dose			X	X	X	X	X	X															X[3]	X[3]
Informed Consent/Assent		X§																						
Screening/ Demographics	*																							
Inclusion/ Exclusion Criteria		X																						
Update Medical History		X																						
Vital Signs/ Weight		**		X		X		X[2]	X	X	X	X[2]	X	X	X	X[2]	X	X	X	X[2]	X		X	
Physical Examination	*									X[4]		X				X				X				
Complete Neurological Exam	*											X				X				X				
Height	*																							
12-lead ECG		X		X		X		X		X	X	X				X				X			X[3,9]	
Blood Sampling for PK																							X[7,8]	
Chemistry/ Hematology/ UA	*							X		X		X				X				X			X[3]	
Blinded CYP2D6 Genotype[1]	*																							
Pregnancy Test		U								U		U				U				U				
AIMS		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Video Recording of AIMS		X						X	X	X	X	X				X				X				
UPDRS Part III - Motor		**		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[3]	

	Screening		Year 1										Year 2				Year 3				Follow-up clinic visit	Follow-up call	Unscheduled	
			Titration Period		Long-Term Treatment Period																			
Study Week‖ →	**Prior Data from Parent Study†**	**Base-line‡**	**1**	**2**	**3**	**4**	**5**	**6**	**15**	**28**	**41**	**54**	**67**	**80**	**93**	**106**	**119**	**132**	**145**	**158[10]/ET[11]**	**159 or 1 week after ET**	**162 or 4 weeks after ET**		
Visit Window (days)		+3	± 1																	± 3				
Activity Visit Type →		V	TC	V	TC	V	TC	V	V	V	V	V	V	V	V	V	V	V	V	V	V	TC	V	TC
BARS		**		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[3]	
HADS		**		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
C-SSRS[5]		**		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
ESS		**		X		X		X	X	X	X	X	X	X	X		X		X	X			X[3]	
CGIC						X		X	X	X	X	X	X	X	X	X	X	X	X					
PGIC						X		X	X	X	X	X	X	X	X	X	X	X	X					
MoCA©		X						X	X	X	X	X	X	X	X		X		X					
Modified CDQ-24		X						X	X	X	X	X				X			X					
Dispense/Order Study Drug[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X[3]	X[3]
Assess Study Drug Accountability/ Compliance				X		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Assess AEs	*		X	X	X	X	X	X	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	X	X	X	X	X
Evaluate Dyskinesia Control (patient/ caregiver)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

SCHEDULE OF EVENTS (Part A) KEY
[V] Clinic Visit
[TC] Telephone Contact
[ET] Early Termination Visit
[U] Urine pregnancy test for women of childbearing potential only
Abbreviations: AEs, adverse events; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CDQ-24, Craniocervical Dystonia Questionnaire; CGIC, Clinical Global Impression of Change; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; ESS Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; MoCA©, Montreal Cognitive Assessment; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; SAE, serious adverse event; UA, urinalysis; UPDRS, Unified Parkinson's Disease Rating Scale.
‖ All stable patients will be invited to participate in Part B after Amendment 06 implementation regardless of current study week. Patients will need to be on a stable dose of SD-809 and any concomitant dopamine receptor antagonist for a minimum of 4 weeks before starting the Double-Blind, Randomized Withdrawal Period.

† After Informed Consent is obtained, prior data from the parent study will be used in this study as part of screening information as detailed in the informed consent/assent.
‡ Data from the Week 13 evaluation of the parent study 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
* Data (Week 12 or earlier) from the parent study will be used in this study as part of screening information.
** Data (Week 13) from the parent study will be used 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 the parent study.
2 Perform orthostatic blood pressure and pulse after patient 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.
6 Study medication supply will be ordered (see Operations Manual for further details).
7 Patients who experience an SAE should have a blood sample collected for pharmacokinetic assessment as soon as possible after the SAE and within 48 hours of last dose of study drug, if possible.
8 Patients who have not achieved adequate control of dyskinesia during the study may have up to two blood samples collected within 48 hours of the last dose of study drug for future pharmacokinetic assessment of α- and β-HTBZ. The pharmacokinetic sampling for inadequate efficacy must be pre-approved by the Medical Monitor.
9 Patients undergoing an increase in dose of their current antipsychotic treatment, switching to a new antipsychotic agent, or having an additional antipsychotic treatment added to their regimen will require additional ECG monitoring (see Section 6.6.1 of the protocol).
10 Patients who have been on a stable dose of SD-809 and any concomitant dopamine receptor antagonist for 4 weeks will be invited to participate in the Randomized Withdrawal Period (Part B). If the patient chooses to participate in Part B, then participation in Part A will end.
11 Patients will complete a follow-up visit 1 week after ET and a follow-up call 4 weeks after ET.

Part B

	Randomized Withdrawal Period		Open-label Treatment	Follow-up			
	Part B Pre-Withdrawal Visit	**Part B Post-Withdrawal Visit[11]**	**EOT[2]/ET**	**Follow-up clinic visit (ET only)**	**Follow-up Call**	**Unscheduled**	
Study Week →	**After Amendment 06 Implementation[1,12]**	**+1 Week**	**12 Weeks after Post-Withdrawal Visit**	**1 Week after ET**	**4 Weeks after EOT/ET**		
Visit Window (days)		+3	±3				
Activity Visit Type →	V	V	V	V	TC	V	TC
Evaluate/Adjust Dose[3]						X[4]	X[4]
Informed Consent/Assent	X[5]						
Randomization via IRT	X						
Screening/ Demographics							
Inclusion/ Exclusion Criteria							
Update Medical History							
Vital Signs/ Weight	X[6]	X	X[6]	X		X	
Physical Examination			X				
Complete Neurological Exam			X				
12-lead ECG	X	X	X			X[4,11]	
Blood Sampling for PK		X				X[9,10]	
Chemistry/ Hematology/ UA	X	X	X			X[4]	
Pregnancy Test	U		U				
AIMS	X	X	X	X			
Video Recording of AIMS	X	X	X				
UPDRS Part III - Motor	X	X	X	X		X[4]	
BARS	X	X	X	X		X[4]	
HADS	X	X	X	X		X	
C-SSRS[7]	X	X	X	X		X	
ESS	X	X	X	X		X[4]	
CGIC							
PGIC							
MoCA©	X	X	X				

	Randomized Withdrawal Period		Open-label Treatment	Follow-up			
	Part B Pre-Withdrawal Visit	**Part B Post-Withdrawal Visit[11]**	**EOT[2]/ET**	**Follow-up clinic visit (ET only)**	**Follow-up Call**	**Unscheduled**	
Study Week →	**After Amendment 06 Implementation[1,12]**	**+1 Week**	**12 Weeks after Post-Withdrawal Visit**	**1 Week after ET**	**4 Weeks after EOT/ET**		
Visit Window (days)		+3	±3				
Activity Visit Type →	V	V	V	V	TC	V	TC
Modified CDQ-24							
Dispense/Order Study Drug[8]	X	X				X[4]	X[3]
Assess Study Drug Accountability/ Compliance[13,14]	X	X	X				
Assess AEs	X	X	X	X	X	X	X
Assess Concomitant Meds	X	X	X	X	X	X	X
Evaluate Dyskinesia Control (patient/caregiver)	X	X	X	X		X	X

SCHEDULE OF EVENTS (Part B) KEY

[V] Clinic Visit
[TC] Telephone Contact
[EOT] End of Treatment
[ET] Early Termination Visit
[U] Urine pregnancy test for women of childbearing potential only

Abbreviations: AEs, adverse events; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CDQ-24, Craniocervical Dystonia Questionnaire; CGIC, Clinical Global Impression of Change; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; ESS Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; IRT, MoCA©, Montreal Cognitive Assessment; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; SAE, serious adverse event; UA, urinalysis; UPDRS, Unified Parkinson's Disease Rating Scale.

1 Assessments required for the Pre-Withdrawal Visit will be those required for the next scheduled visit, or visit as determined by the Investigator, after Amendment 06 implementation and patient consent for Part B.
2 The EOT visit will occur 12 weeks after the Post-Withdrawal Visit.
3 Titration is not permitted during the Randomized Withdrawal Period and will be allowed after return to open-label dosing.
4 Assessments to be completed at Investigator's discretion.
5 Patients who do not sign the informed consent for Part B will continue participation in Part A. Patients who decline participation in Part B will be given an ongoing option to participate at subsequent study visits.
6 Perform orthostatic blood pressure and pulse.
7 The C-SSRS Since Last Visit version is administered at all visits.
8 Study medication supply will be ordered (see Operations Manual for further details).

[9] At the discretion of the Principal Investigator and/or Medical Monitor, patients who experience an SAE may have a blood sample collected for pharmacokinetic assessment after experiencing the SAE. All such blood samples will be collected within 48 hours of last dose of study drug.

[10] Patients who have not achieved adequate control of dyskinesia during the study may have up to two blood samples collected within 48 hours of the last dose of study drug for future pharmacokinetic assessment of α- and β-HTBZ. The pharmacokinetic sampling for inadequate efficacy must be pre-approved by the Medical Monitor.

[11] Patients undergoing an increase in dose of their current antipsychotic treatment, switching to a new antipsychotic agent, or having an additional antipsychotic treatment added to their regimen will require additional ECG monitoring (see Section 6.6.1 of the protocol).

[12] If the patient chooses to participate in Part B, the first visit will be the patient's next scheduled visit, or as soon as possible, as determined by the Investigator, after Amendment 06 implementation. The Post-Withdrawal Visit will occur 1 week (+3 days maximum). If the Post-Withdrawal Visit is >3 days beyond the 1 week time period, the patient may be required to undergo titration, as decided by the Investigator in consultation with the Medical Monitor (if necessary) per the guidelines in Table 3 of the protocol. After the Randomized Withdrawal Period, the patient will continue on or return to previous (before placebo) SD-809 dose.

[13] Prior to the Pre-Withdrawal Visit, the Investigator or designated site staff must place a call to remind the patient to bring all remaining study drugs to the visit. The Investigator or designated site staff must collect the study drug(s) from the patient and conduct drug accountability.

[14] Prior to the Post-Withdrawal Visit, the Investigator or designated site staff must place a call to remind the patient to bring all remaining study drugs to the visit. The Investigator or designated site staff must collect the study drug(s) from the patient and conduct drug accountability.

2.2. Primary and Secondary Measures and Endpoints

2.2.1. Safety Measures and Endpoints

The safety measures and endpoints in Part A are as follows:

1. Incidence of AEs, SAEs, severe AEs, drug related AEs, AEs leading to withdrawal, AEs leading to dose reduction, AEs leading to dose suspension during the following periods: overall, during titration, and during long-term treatment
2. Observed values and changes from baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis)
3. Observed values and changes from baseline in vital signs
4. Observed values in electrocardiogram (ECG) parameters and abnormal findings
5. Number of patients with on-treatment QTcF (Fridericia-corrected QT interval) values >450 ms, >480 ms, >500 ms, or a change from baseline in QTcF of >30 ms or >60 ms.
6. Observed values and changes in Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor examination), Barnes Akathisia Rating Scale (BARS), Hospital Anxiety and Depression Scale (HADS), Columbia-Suicide Severity Rating Scale (C-SSRS), Epworth Sleepiness Scale (ESS), and MoCA© (Montreal Cognitive Assessment)

The safety measures and endpoints in Part B (Randomized Withdrawal Period) are as follows:

1. Incidence of adverse events, serious adverse events, drug-related adverse events, and adverse events leading to withdrawal.
2. Observed values and changes from start of randomized withdrawal in clinical laboratory parameters (hematology, chemistry, and urinalysis)
3. Observed values and changes from start of randomized withdrawal in vital signs
4. Observed values in electrocardiogram (ECG) parameters and abnormal findings
5. Number of patients with on-treatment QTcF (Fridericia-corrected QT interval) values >450 ms, >480 ms, >500 ms, or a change from baseline in QTcF of >30 ms or >60 ms.
6. Observed values and changes in UPDRS Part III (motor examination), BARS, HADS, C-SSRS, ESS, and MoCA©

2.2.2. Efficacy Measures and Endpoints

The efficacy measures and endpoints in Part A are as follows:

AIMS:

- The change in total motor AIMS score (items 1 through 7) from Baseline of this study at each visit that this is measured, as assessed by the site rating.
- The percent change in total motor AIMS score from Baseline of this study at each visit that this is measured.

- The proportion of patients who have a 50% or greater reduction in total motor AIMS score from Baseline of this study at each visit that this is measured.
- The proportion of patients who have a 70% or greater reduction in total motor AIMS score from Baseline of this study at each visit that this is measured.
- The change in AIMS items 8, 9, and 10 from Baseline of this study to each visit that this is measured.

CGIC:

- The proportion of patients who are a treatment success, based on the CGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the CGIC from Baseline of this study.

PGIC:

- The proportion of patients who are a treatment success, based on the PGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the PGIC from Baseline of this study.

mCDQ-24:

- The change in mCDQ-24 (Modified Craniocervical Dystonia Questionnaire) from Baseline of this study at each visit that this is measured.

The efficacy measure and endpoint in Part B is as follows:

- Primary efficacy endpoint: change from Pre-Withdrawal Visit total motor AIMS score as assessed by blinded central video rating to the Post-Withdrawal Visit between patients treated with SD-809 and patients treated with placebo.

2.3. Sample Size and Power Considerations

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

It is estimated that approximately 91 patients per arm in the Randomized Withdrawal Period will enable a power of at least 90% to detect a beneficial effect of 1.4 points or more in the change from pre-withdrawal to post-withdrawal in centrally read AIMS when the SD-809 arm is compared to placebo, assuming a standard deviation of 2.9 and a 2-sided type I error rate of 5%.

At the time of finalizing this SAP, all patients have started Part B, or completed part A, or have withdrawn from Part A. 143 patients were randomized to Part B, resulting in a power of approximately 80%.

2.4. Randomization and Blinding

At the beginning of the Randomized Withdrawal Period, patients will be randomized in a blinded fashion to either SD-809 (current dose) or placebo in a 1:1 ratio stratified by DRA status.

2.5. Sequence of Planned Analyses

2.5.1. Interim Analyses 1

The first interim analysis was conducted for the purpose of preparing the integrated summary of safety for the NDA submission. The interim analysis will be based on patient data accrued as of 30-Jun-2016.

2.5.2. Interim Analyses 2

A second interim analysis was conducted for the purpose of preparing an integrated summary of safety. The interim analysis was based on patient data accrued as of 1-Dec-2018.

2.5.3. Final Analyses and Reporting – Part A and B

Final analyses for Part A and B of this study will be performed after the last patient that enrolled into Part B has completed Part B of the study.

3. POPULATIONS /ANALYSIS SETS

3.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all patients who were enrolled in the study, regardless of whether or not a patient received a dose of study drug.

3.2. Safety Population

The Safety population will include all patients who were administered any study drug. Patients who were enrolled but withdrew prior to dosing will not be included in the safety population.

3.3. Randomized Withdrawal ITT Population

The randomized withdrawal ITT population will include all patients enrolled in Part B of the study.

3.4. Randomized Withdrawal Modified Intent-to Treat Population

The randomized withdrawal modified intent-to-treat (mITT) population will include all patients enrolled in Part B who receive study drug during the Randomized Withdrawal Period and have a total motor AIMS score as assessed by blinded central video rating at both the Pre-Withdrawal Visit and the Post-Withdrawal Visit.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation, standard error, median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages.

4.2. Specification of Baseline Values

Baseline of this study is the last observed data on or prior to the first dose of drug in the present study (SD-809-C-20). Some of the data used for baseline of this study will come from the parent study (see Table 1). For baseline data that is coming from the parent study, baseline of this study will be the last observed data collected during the follow-up phase of the parent study. If data are not collected or are missing during the follow-up period in the parent study, then baseline of this study will be the last observed data on or prior to the first dose of drug in the parent study.

4.3. Scoring for Rating Scales

A detailed description for all rating scales below can be found in the protocol.

The AIMS is composed of 12 clinician-administered and scored items. The total motor AIMS score is the sum of items 1 through 7.

The mCDQ-24 is composed of 24 self-administered questions and has 5 domains. The mCDQ-24 questions are rated on a 5-point scale from 0 (never or not at all) to 4 (always or very severely). Patients are instructed to indicate how they felt during the past two weeks because of their abnormal movements by selecting one of the five statements for each question. Following are the domains assessed in the mCDQ-24:

- Stigma (questions 7, 8, 9, 10, 18, 22)
- Emotional wellbeing (questions 11, 12, 13, 14, 15)
- Pain (questions 4, 5, 21)
- ADL (questions 1, 2, 3, 6, 19, 20)
- Social/family life (questions 16, 17, 23, 24)

Each raw domain score is calculated as the sum of the questions in the particular domain. For each domain, raw sub-scores (sum of the individual question scores) will be calculated and then linearly transformed to a 0–100 scale, where a score of 0 indicates the best and a score of 100 the worst possible score. The total score (sum of the raw sub-scores) is similarly transformed to a 0–100 scale (best to worst score).

The UPDRS motor (part III) consists of the 27 questions related to motor functions in part III of the UPDRS scale. Each of the ratings is assessed on a 5-point scale from 0 to 4, with higher values indicating increasing severity/intensity/frequency. The UPDRS motor score is the sum of the 27 questions in part III. The UPDRS subscale scores are balance (items 27, 30), bradykinesia (items 19, 31), movements (items 23A-B, 24A-B, 25A-B, 26A-B), posture and gait (items 28,

29), rigidity (items 22A-E), speech (item 18), and tremor (20A-E, 21A-B). The subscale scores are calculated as the sum of the individual items.

The BARS is composed of 4 items: an objective assessment of akathisia, two subjective measures (self-awareness of restlessness and distress related to restlessness), and a global clinical assessment. The objective assessment of akathisia, and subjective assessments of self-awareness, restlessness and distress related to restlessness are assessed on a 4-point scale from 0-3, with higher values indicating increasing severity/intensity/frequency. A summary score is calculated based on these 3 items resulting in a total score ranging from 0 to 9. The Global Clinical Assessment of Akathisia uses a 6-point scale ranging from 0 (absent) – 5 (severe).

The HADS is composed of 14 items, 7 each for anxiety and depression. The anxiety subscale is the sum of items 1, 3, 5, 7, 9,11, and 13, and the depression subscale is the sum of items 2, 4, 6, 8, 10, 12, and 14.

The ESS is composed of 8 self-administered questions on a 4-point Likert scale (0 to 3). The ESS total score is the sum of 8 questions and can range between 0 and 24 with higher scores indicating a higher level of daytime sleepiness.

The MoCA© is composed of 11 items. The MoCA© total score is the sum of the 11 items. Item 11 is used to correct for patients with 12 years of education (or less) and is only included in the sum when total score is <30. The maximum total possible score is 30 points, indicating no cognitive impairment.

4.4. Handling Withdrawals and Missing Data

Data summarization for a visit will be based on observed data only.

For AIMS assessed by the site rating, if a response to 1 question is missing, the missing response will be replaced with the average of the remaining responses. If responses to 2 or more questions are missing, the missing responses will not be replaced and the total score will be set to missing.

For mCDQ-24, if a response to 1 question within a domain is missing, the missing response will be replaced with the average of the remaining responses within the domain; if responses to 2 or more questions within a domain are missing, the missing responses will not be replaced and the domain score will be set to missing; if at least 1 domain score is missing then the total score will be set to missing.

For UPDRS motor (part III), if responses to 5 or fewer questions are missing, the missing responses will be replaced with the average of the remaining responses. If responses to 6 or more questions are missing, the missing responses will not be replaced and the total score will be set to missing.

For HADS, if a response to 1 question within a subscale is missing, the missing response will be replaced with the average of the remaining responses within the subscale. If a response to 2 or more questions within a subscale are missing, the missing responses will not be replaced and the subscale score will be set to missing.

For ESS, if responses to 2 or fewer questions are missing, the missing responses will be replaced with the average of the remaining responses. If responses to 3 or more questions are missing, the missing responses will not be replaced and the total score will be set to missing.

For all other rating scales, if any response is missing then the total or subscale score will be set to missing.

4.5. Study Days and Visit Windows

Study days will be numbered relative to the 1st day of study drug administration. The start of treatment (day 1) is defined as the date on which a patient takes the 1st dose of study drug. Days will be numbered relative to study start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the start of study drug and day –1 being the day before the start of study drug).

Part A Visits:

For efficacy and safety by-visit analyses, data collected at post baseline scheduled visits will be included using their scheduled visit and data collected at early termination and unscheduled visits will be included and assigned to a visit window as described below. After the assignments are made use the following rules: if there is a scheduled visit with an early termination and/or unscheduled visit in the same visit window, the scheduled visit will be used in the analysis; if there is no scheduled visit but an early termination and unscheduled visit in the same visit window, the early termination visit will be used in the analysis; if there is no scheduled or early termination visit but an unscheduled visit in a visit window, the unscheduled visit will be used in the analysis.

Efficacy: Visit Windows for Early Termination and Unscheduled Visits

	Study Day		
Visit	**AIMS site**	**CGIC, PGIC**	**mCDQ-24**
Week 2	2 to 21		
Week 4	22 to 35	2 to 35	
Week 6	36 to 74	36 to 74	2 to 74
Week 15	75 to 151	75 to 151	75 to 151
Week 28	152 to 242	152 to 242	152 to 242
Week 41	243 to 328	243 to 328	243 to 328
Week 54	329 to 424	329 to 424	329 to 560
Week 67	425 to 515	425 to 515	
Week 80	516 to 606	516 to 606	
Week 93	607 to 697	607 to 697	
Week 106	698 to 788	698 to 788	561 to 924
Week 119	789 to 879	789 to 879	
Week 132	880 to 970	880 to 970	
Week 145	971 to 1061	971 to 1061	
Week 158	1062 to 1110	≥1062	≥925
Follow-up	≥1111		

Safety: Visit Windows for Early Termination and Unscheduled Visits

	Study Day						
Visit	**[1]**	**[2]**	**[3]**	**[4]**	**[5]**	**[6]**	**[7]**
Week 2	2 to 21	2 to 21				2 to 21	2 to 21
Week 4	22 to 35	22 to 35				22 to 67	22 to 35
Week 6	36 to 74	36 to 119	2 to 119	2 to 74	2 to 210		36 to 74
Week 15	75 to 151			75 to 151		68 to 151	75 to 151
Week 28	152 to 242	120 to 242	120 to 287	152 to 242		152 to 242	152 to 242
Week 41	243 to 328	243 to 328		243 to 328		243 to 378	243 to 328
Week 54	329 to 424	329 to 560	288 to 560	329 to 424	211 to 560		329 to 424
Week 67	425 to 515			425 to 515		379 to 515	425 to 515
Week 80	516 to 606			516 to 606		516 to 606	516 to 606
Week 93	607 to 697			607 to 697		607 to 742	607 to 697
Week 106	698 to 788	561 to 924	561 to 924	698 to 833	561 to 924		698 to 833
Week 119	789 to 879					743 to 879	
Week 132	880 to 970			834 to 1015		880 to 970	834 to 1015
Week 145	971 to 1061					971 to 1110	
Week 158	1062 to 1110	≥925	≥925	≥1016	≥925		≥1016
Follow-up	≥1111					≥1111	

[1] Vital signs, weight, UPDRS, BARS, HADS, C-SSRS; [2] ECG; [3] Laboratory tests; [4] MoCA©; [5] Standing, Supine, and Orthostatic heart rate and blood pressure; [6] Sitting heart rate and blood pressure; [7] ESS.

Part B Visits:

For efficacy and safety by-visit analyses, data collected at the ET visit during open-label treatment will be included and assigned to the EOT visit. Data collected at unscheduled visits during open-label treatment will not be included in any analyses.

Part A and B Combined:

Some analyses, such as the analyses of adverse events, will be performed by time period. For these analyses, the following definitions will be used:

- Titration Period - from the first dose of treatment until 7 days after the week 6 visit. If a patient discontinues treatment before 7 days after the week 6 visit, then the Titration Period is until the last dose of treatment.
- Maintenance Period - from 8 days after the week 6 visit until the day of the week 158 visit for patients only in Part A and until the day of the open-label treatment EOT visit for patients in both Parts A and B. If a patient enters the Maintenance Period but discontinues treatment early, the Maintenance Period is until the last dose of treatment.

- Overall Treatment Period - includes the Titration and the Maintenance Periods, if applicable.
- Follow-up Period - from the end of the Overall Treatment Period through the end of the study.

5. STUDY POPULATION

5.1. Part A

5.1.1. General

The ITT population will be used for all study population summaries. Summaries will be presented by parent study treatment group (prior SD-809 and prior placebo) and overall.

5.1.2. Patient Disposition

Patients in the ITT population, patients in the ITT population but not treated, patients in the safety population, patients in the randomized withdrawal ITT and randomized withdrawal mITT populations, patients who completed Parts A and B and the study, patients who withdrew from Parts A and B and the study, and patients who enrolled in Part C will be summarized using descriptive statistics. Patients who withdrew from Parts A and B and the study will also be summarized using descriptive statistics by reason for withdrawal.

The Part A visit when patients enrolled in Part B will be summarized using descriptive statistics.

Patients reaching each Part A visit will be summarized using descriptive statistics.

Reasons for withdrawal by Part A visits using the categories prior to week 54 visit, week 54 visit to before week 106 visit, and week 106 visit to before week 145 visit will be summarized using descriptive statistics.

5.1.3. Demographics and Baseline Characteristics

The continuous variables of patient age, weight, height, and body mass index (BMI), all collected at baseline in the parent study, will be summarized using descriptive statistics. The categorical variables of patient sex, race, ethnicity, and education (≤12 or >12 years) (collected at baseline in the parent study) will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

The continuous variables of time since tardive dyskinesia diagnosis in years, baseline total motor AIMS score, and baseline mCDQ-24 total score, all determined from baseline in the parent study, will be summarized using descriptive statistics. The categorical variables of baseline use of DRA (Yes/No), background comorbid illness types, use of a strong CYP2D6 inhibitor (Yes/No), poor CYP2D6 metabolizer (Yes/No), and impaired CYP2D6 function (Yes/No), all determined from baseline in the parent study, will be summarized using descriptive statistics for each category.

Strong CYP2D6 inhibitor status was determined by classifying patients as taking versus not taking a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion) at baseline in the parent study. Impaired CYP2D6 function was defined as use of a strong CYP2D6 inhibitor at baseline in the parent study and/or a poor CYP2D6 metabolizer.

5.1.4. Prior Medications

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug). The incidence of prior medications will be summarized using descriptive statistics by therapeutic class and preferred term. The therapeutic class will be displayed as the ATC3 code if available or the most specific ATC code if ATC3 is not available. The preferred term is displayed as the collapsed preferred term (single generic ingredients collapsed to base substance preferred term). Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken prior to the first day of study drug treatment.

5.1.5. Protocol Deviations

Patients with at least 1 protocol deviation as recorded on the CRF, and protocol deviations for each category will be summarized using descriptive statistics.

5.2. Part B

5.2.1. General

The randomized withdrawal ITT population will be used for all Part B study population summaries. Summaries will be presented by randomized withdrawal treatment group (SD-809 and placebo) and overall.

5.2.2. Patient Disposition

Patients in the randomized withdrawal ITT and randomized withdrawal mITT populations, patients who completed Part B, and patients who withdrew during Part B will be summarized using descriptive statistics. Patients who withdrew during Part B will also be summarized using descriptive statistics by reason for withdrawal.

5.2.3. Demographics and Baseline Characteristics

The continuous variables of patient age, weight, and body mass index (BMI) (all collected at the Pre-Withdrawal Visit, and height (collected at baseline in the parent study) will be summarized using descriptive statistics. The categorical variables of patient sex, race, ethnicity, and education (≤12 or >12 years) (collected at the Pre-Withdrawal Visit) will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

The continuous variables of time since tardive dyskinesia diagnosis (calculated at the Pre-Withdrawal Visit) and pre-withdrawal total motor AIMS score will be summarized using descriptive statistics. The categorical variables of pre-withdrawal use of DRA (Yes/No), pre-withdrawal use of CYP2D6 inhibitors, and pre-withdrawal use of a strong CYP2D6 inhibitor (Yes/No) will be summarized using descriptive statistics for each category.

Strong CYP2D6 inhibitor status was determined by classifying patients as taking versus not taking a strong CYP2D6 inhibitor (paroxetine, fluoxetine, or bupropion) at the Pre-Withdrawal Visit.

6. EFFICACY ANALYSIS

6.1. Part A

6.1.1. General

The ITT population will be used for all efficacy summaries. Summaries will be presented by parent study treatment group and overall for Part A visits.

All continuous efficacy endpoints will be summarized for actual values and changes (or percent changes) from baseline of this study to each visit using descriptive statistics.

All categorical efficacy endpoints will be summarized at each visit using descriptive statistics. In addition, the CGIC and PGIC ratings at each visit will be summarized using descriptive statistics.

The mCDQ-24 domain scores will also be summarized for actual values and changes from baseline of this study to each visit using descriptive statistics.

No inferential statistics will be presented for efficacy endpoints.

6.2. Part B

6.2.1. General

The randomized withdrawal mITT population will be used for the efficacy analysis in Part B. The summaries will be presented by randomized withdrawal treatment group and overall, unless otherwise noted.

6.2.2. Efficacy Variables and Analyses

The primary efficacy variable is the change in total motor AIMS score as assessed by blinded central video rating from Pre-Withdrawal Visit to Post-Withdrawal Visit

Analysis of the change in total motor AIMS score as assessed by blinded central video rating during the Randomized Withdrawal Period (from the Pre-Withdrawal Visit to the Post-Withdrawal Visit) will use an analysis of covariance (ANCOVA) model with the change in total motor AIMS score as the dependent variable. The model will include randomized withdrawal treatment group and DRA status at the Pre-Withdrawal Visit as fixed effects, and the total motor AIMS score at the Pre-Withdrawal Visit value as a covariate. The least squares means of the change in total motor AIMS score will be compared between the SD-809 treatment and placebo groups using a 2-sided test at the alpha=0.05 level of significance. The SAS code for this test is as follows:

The least square (LS) mean and standard error for the treatment groups, and the LS mean difference, 95% confidence interval (CI), and p-value for the comparison (SD-809 vs. placebo) will be presented at the Post-Withdrawal Visit.

Total motor AIMS score values (central reading) and changes from the Pre-Withdrawal Visit to the Post-Withdrawal Visit and EOT visit will be summarized using descriptive statistics for each treatment group. The overall summary will not be presented at the Post-Withdrawal Visit.

In addition, total motor AIMS score (site rating) values and changes from the Pre-Withdrawal Visit to the Post-Withdrawal Visit and EOT visit will be summarized using descriptive statistics for each treatment group. The overall summary will not be presented at the Post-Withdrawal Visit.

7. SAFETY ANALYSIS

7.1. Part A

7.1.1. General

The safety population will be used for all safety summaries. Summaries will be presented by parent study treatment group and overall. Summaries will be presented for Parts A and B combined unless otherwise noted.

7.1.2. Study Drug Administration

Duration of treatment (days treated) is the number of days on treatment based on the first and last day of treatment with the study drug (last day of study drug – first day of study drug + 1). Weeks on treatment using the categories ≥2 weeks, ≥4 weeks, ≥6 weeks, ≥15 weeks, ≥28 weeks, ≥41 weeks, ≥54 weeks, ≥67 weeks, ≥80 weeks, ≥93 weeks, ≥106 weeks, ≥119 weeks, ≥132 weeks, ≥145 weeks, ≥158 weeks and ≥171 weeks will be summarized using descriptive statistics. Duration of treatment (days) will also be summarized as continuous data using descriptive statistics.

Total daily dose (mg) will be summarized as continuous data at each Part A visit using descriptive statistics. In addition, total daily dose (mg) will be summarized by individual dose and dose categories (<24 mg, ≥24 to ≤36 mg, >36 to ≤48 mg, and >48 mg) as categorical data at each Part A visit using descriptive statistics.

Percent treatment compliance is calculated as 100*(number of tablets used / number of tablets expected to be used). The number of tables used is the number of tablets dispensed minus the number of tablets returned. If a patient does not return the pill bottle, it will be assumed that the patient took no study medication from that bottle for the purposes of calculating compliance. The number of tablets expected to be used is based on the number of morning and evening dosing times during the treatment period (1 tablet is used for each dosing time point). A patient will be deemed compliant over the treatment period if the patient has taken 80% to 105% of the expected tablets of study drug.

Percent treatment compliance will be summarized as continuous data using descriptive statistics. In addition, percent treatment compliance will be summarized as categorical data using descriptive statistics for the following categories: <80%, 80% to 105%, >105%.

7.1.3. Adverse Events

All AEs will be coded using MedDRA. Summaries will be presented in the overall treatment period (titration plus maintenance treatment period) for all AEs (overall and by severity), AEs determined by the investigator to be treatment-related, serious AEs, AEs causing discontinuation from the study, non-serious AEs, AEs leading to dose reduction, and AEs leading to dose suspension. In addition, all AEs will be summarized separately for the titration period, maintenance treatment period, and follow-up period.

All AEs in the overall treatment period will be summarized by strong CYP2D6 inhibitor status (Yes/No), poor CYP2D6 metabolizer phenotype status (Yes/No), impaired CYP2D6 function

status (Yes/No), baseline use of DRA status (Yes/No), and background comorbid illness type. In addition, serious AEs and AEs by severity will be summarized by impaired CYP2D6 function status.

The incidence of adverse events will be summarized using descriptive statistics by system organ class and preferred term. Patients are counted only once in each system organ class category and only once in each preferred term category. For all AEs in the overall treatment period, the event rate will also be presented. The event rate is defined as 100*(total number of AEs / patient years of treatment in Parts A and B combined). Treatment-related adverse event summaries will include adverse events with possible, probable, definite, or missing relationship to study drug. For the summaries by severity, patients are counted at the greatest severity only once in each system organ class category and only once in each preferred term category.

The Standard MedDRA Queries (SMQs) of depression (excl suicide and self injury), suicide/self-injury, akathisia, Parkinson-like events, and Torsade de pointes/QT prolongation AEs, and somnolence and sedation AEs of interest as specified in Appendix A will be summarized using descriptive statistics. In addition, time to first SMQ AE or AE of interest will be presented using Kaplan-Meier curves for each SMQ AE or AE of interest. For this analysis, patients who do not experience the event will be censored at the end of treatment in Parts A and B combined.

In addition, the exposure-adjusted incidence rate (EAIR) of AEs in the overall treatment period will be presented for the overview of AEs, AEs by SOC and preferred terms, and the SMQ summaries. EAIR is calculated as the number of patients with an AE divided by patient-years of treatment. For calculating patient years, patients with an AE contribute with treatment exposure up to the day of their first AE, patients without an AE contribute their entire treatment duration in Parts A and B combined as described above for the censoring if patients do not experience an event.

The EAIR for all AEs in the overall treatment period and for SMQ categories will be summarized by the time periods of <15 weeks, ≥15 to <54 weeks, ≥54 to <106 weeks, ≥106 to <158 weeks, and ≥158 weeks using descriptive statistics.

All AEs in the overall treatment period that occurred in ≥4% of patients will be summarized by preferred term using descriptive statistics.

Listings for AEs leading to death, serious AEs, AEs causing discontinuation, AEs leading to dose reduction, and AEs leading to dose suspension will be presented.

7.1.4. Deaths

If any patient dies during the study all relevant information will be discussed in the patient's narratives included in CSR.

7.1.5. Clinical Laboratory Tests

Summary statistics for serum, chemistry, hematology, and urinalysis laboratory tests will be presented at baseline of this study and each Part A visit that this is measured using standard international units. Serum chemistry laboratory tests will also be presented using conventional units. Laboratory tests values and changes from baseline of this study to each visit will be

summarized using descriptive statistics. Shifts (below, within, and above the normal range) from baseline of the parent study to each Part A visit will be summarized using patient counts.

7.1.6. Vital Signs

Summary statistics for resting heart rate and blood pressure, respiration rate, temperature, and weight will be presented at baseline of this study and at each Part A visit that these are measured. Summary statistics for orthostatic heart rate and blood pressure will be presented at baseline of this study and each Part A visit that this is measured. Vital signs values and changes from baseline to each visit the vital sign is measured will be summarized using descriptive statistics.

Orthostatic changes in heart rate and orthostatic changes in blood pressure vital signs values are calculated as the standing minus supine value at the same visit.

7.1.7. Electrocardiogram

Shifts (normal, abnormal not clinically significant, and abnormal clinically significant) from baseline of this study to each Part A visit that this is measured will be summarized using patient counts.

The number of patients with postbaseline QTcF values >450 ms, >480 ms, >500 ms, or a change from baseline in QTcF of >30 ms or >60 ms, PR interval values >200 ms, QRS duration values >100 ms, and QT interval values >500 ms will be summarized using descriptive statistics. This summary will be repeated for patients who have a normal QTcF at baseline according to the protocol definition.

7.1.8. Physical Examination

A listing will be presented for all physical examination data.

7.1.9. Neurological Examination

A listing will be presented for all neurological examination data.

7.1.10. Concomitant Medications

All concomitant medications will be coded using the WHO Drug. The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Concomitant medications will include all medications taken while the patient takes study drug.

In addition, separate summaries will be presented including only concomitant medications prior to baseline and concomitant medications that started post baseline.

7.1.11. Other Safety Assessments

Summary statistics for the UPDRS motor score and subscale scores will be presented at baseline of this study and each Part A visit that this is measured. UPDRS motor score and subscale scores values and changes from baseline of this study to each visit will be summarized using descriptive statistics.

Summary statistics for the BARS summary score will be presented at baseline of this study and each Part A visit that this is measured. BARS summary score values and changes from baseline of this study to each visit will be summarized using descriptive statistics.

Summary statistics for the HADS depression and anxiety subscales scores will be presented at baseline of this study and each Part A visit that this is measured. HADS subscale values and changes from baseline of this study to each visit will be summarized using descriptive statistics.

Summary statistics for the C-SSRS baseline version will be presented at screening and for the C-SSRS last visit version will be presented at baseline of this study and each Part A visit that this is measured. Patients with suicidal ideation and behavior items as well as self-injurious behavior without suicidal intent will be summarized at each visit as categorical data using descriptive statistics.

Also for C-SSRS, patients with suicidal ideation and behavior items as well as self-injurious behavior without suicidal intent will be summarized at anytime postbaseline as categorical data using descriptive statistics. Shifts (yes, no) from baseline of this study to anytime postbaseline will be summarized using patient counts for the suicidal ideation and behavior categories as well self-injurious behavior without suicide intent.

Summary statistics for the ESS total score will be presented at baseline of this study and each Part A visit that this is measured. ESS total score values and changes from baseline of this study to each visit will be summarized using descriptive statistics.

Summary statistics for the MoCA© total score will be presented at baseline of this study and each Part A visit that this is measured. MoCA© total score values and changes from baseline of this study to each visit will be summarized using descriptive statistics.

7.2. Part B

7.2.1. General

The randomized withdrawal ITT population will be used for all Part B safety summaries. Summaries will be presented by randomized withdrawal treatment group (SD-809 and placebo) and overall for Part B visits.

7.2.2. Study Drug Administration

Total daily dose (mg) will be summarized as continuous data at each Part B visit using descriptive statistics.

7.2.3. Adverse Events

All AEs in the Part B Randomized Withdrawal Period will be summarized using descriptive statistics by system organ class and preferred term.

7.2.4. Clinical Laboratory Tests

Summary statistics for serum, chemistry, hematology, and urinalysis laboratory tests will be presented at the Pre-Withdrawal Visit and each Part B visit that this is measured using standard international units. Serum chemistry laboratory tests will also be presented using conventional units. Laboratory tests values and changes from the Pre-Withdrawal Visit to each visit will be

summarized using descriptive statistics. Shifts (below, within, and above the normal range) from the Pre-Withdrawal Visit to each Part B visit will be summarized using patient counts.

7.2.5. Vital Signs

Summary statistics for resting heart rate and blood pressure, respiration rate, temperature, and weight will be presented at the Pre-Withdrawal Visit and at each Part B visit that these are measured. Summary statistics for orthostatic heart rate and blood pressure will be presented at the Pre-Withdrawal Visit and each Part B visit that this is measured. Vital signs values and changes from the Pre-Withdrawal Visit to each visit the vital sign is measured will be summarized using descriptive statistics.

Orthostatic changes in heart rate and orthostatic changes in blood pressure vital signs values are calculated as the standing minus supine value at the same visit.

7.2.6. Electrocardiogram

Shifts (normal, abnormal not clinically significant, and abnormal clinically significant) from the Pre-Withdrawal Visit to each Part B visit that this is measured will be summarized using patient counts.

7.2.7. Other Safety Assessments

Summary statistics for the UPDRS motor score and subscale scores will be presented at the Pre-Withdrawal Visit and each Part B visit that this is measured. UPDRS motor score and subscale scores values and changes from the Pre-Withdrawal Visit to each visit will be summarized using descriptive statistics.

Summary statistics for the BARS summary score will be presented at the Pre-Withdrawal Visit and each Part B visit that this is measured. BARS summary score values and changes from the Pre-Withdrawal Visit to each visit will be summarized using descriptive statistics.

Summary statistics for the HADS depression and anxiety subscales scores will be presented at the Pre-Withdrawal Visit and each Part B visit that this is measured. HADS subscale values and changes from the Pre-Withdrawal Visit to each visit will be summarized using descriptive statistics.

Summary statistics for the C-SSRS last visit version will be presented at the Pre-Withdrawal Visit and each Part B visit that this is measured. Patients with suicidal ideation and behavior items as well as self-injurious behavior without suicidal intent will be summarized at each visit as categorical data using descriptive statistics.

Summary statistics for the ESS total score will be presented at the Pre-Withdrawal Visit and each Part B visit that this is measured. ESS total score values and changes from the Pre-Withdrawal Visit to each visit will be summarized using descriptive statistics.

Summary statistics for the MoCA© total score will be presented at the Pre-Withdrawal Visit and each Part B visit that this is measured. MoCA© total score values and changes from the Pre-Withdrawal Visit to each visit will be summarized using descriptive statistics.

8. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

9. CHANGES TO PROTOCOL SPECIFIED ANALYSES

ECG variables at each visit will not be analyzed in this study.

APPENDIX A. SMQ CATEGORIES ADVERSE EVENTS AND ADVERSE EVENTS OF INTEREST

Depression (excl suicide and self injury) (SMQ) – narrow search

Activation syndrome
Adjustment disorder with depressed mood
Adjustment disorder with mixed anxiety and depressed mood
Agitated depression
Anhedonia
Antidepressant therapy
Childhood depression
Decreased interest
Depressed mood
Depression
Depression postoperative
Depressive symptom
Dysphoria
Electroconvulsive therapy
Feeling guilty
Feeling of despair
Feelings of worthlessness
Helplessness
Major depression
Menopausal depression
Post stroke depression
Postictal depression
Postpartum depression

Suicide/self-injury (SMQ) – narrow search

Completed suicide
Depression suicidal
Intentional overdose
Intentional self-injury
Poisoning deliberate
Self-injurious behaviour
Self-injurious ideation
Suicidal behaviour
Suicidal ideation
Suicide attempt

Akathisia (SMQ) – narrow and broad search

Akathisia
Extrapyramidal disorder
Hyperkinesia
Hyperkinesia neonatal
Motor dysfunction

Movement disorder
Psychomotor hyperactivity
Restlessness

Parkinson-like events (SMQ) – narrow and broad search

Action tremor
Akinesia
Bradykinesia
Bradyphrenia
Cogwheel rigidity
Drooling
Dysphonia
Extrapyramidal disorder
Freezing phenomenon
Gait disturbance
Hypertonia
Hypertonia neonatal
Hypokinesia
Hypokinesia neonatal
Masked facies
Micrographia
Mobility decreased
Motor dysfunction
Movement disorder
Muscle rigidity
Muscle tone disorder
Musculoskeletal stiffness
On and off phenomenon
Parkinson's disease
Parkinson's disease psychosis
Parkinsonian crisis
Parkinsonian gait
Parkinsonism rest tremor
Parkinsonism
Parkinsonism hyperpyrexia syndrome
Postural reflex impairment
Postural tremor
Resting tremor
Tremor
Tremor neonatal
Walking disability

Somnolence and sedation – preferred terms

Sedation
Somnolence
Sopor
Stupor

Lethargy

Torsade de pointes/QT prolongation (SMQ) – narrow and broad search

Cardiac arrest
Cardiac death
Cardiac fibrillation
Cardio-respiratory arrest
Electrocardiogram QT interval abnormal
Electrocardiogram QT prolonged
Electrocardiogram U-wave abnormality
Electrocardiogram repolarization abnormality
Long QT syndrome
Long QT syndrome congenital
Loss of consciousness
Sudden cardiac death
Sudden death
Syncope
Torsade de pointes
Ventricular arrhythmia
Ventricular fibrillation
Ventricular flutter
Ventricular tachyarrhythmia
Ventricular tachycardia