Statistical Analysis Plan

An Open-Label, Long-Term Safety, Tolerability, and Efficacy Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents (Open RECLAIM-DCP)

Study Number TV50717-CNS-30081

NCT04200352

SAP Approval Date: 08 July 2022

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(Open RECLAIM-DCP)

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Short title: Reduction of Childhood and Adolescent Abnormal Involuntary Movements in Patients with Dyskinetic Cerebral Palsy in Children and Adolescents (Open RECLAIM-DCP)

Lay person title: A Study to Test if TEV-50717 is Safe and Effective in Relieving Abnormal Involuntary Movements in Cerebral Palsy

Phase 3

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: TV50717-CNS-30081

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Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

Author: [redacted] **Teva Global Statistics**

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Executed signature pages are maintained separately within the Trial Master File/Teva's repository

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADL	activities of daily living
BMI	body mass index
bpm	beats per minute
C-SSRS	Columbia-Suicide Severity Rating Scale
CaGI-I	Caregiver Global Impression of Improvement
CBCL	Child Behavior Checklist (for ages 6-18)
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
COPM	Canadian Occupational Performance Measure
COVID-19	coronavirus disease 2019
CP	cerebral palsy
CRF	case report form
CSR	clinical study report
CTMS	Clinical Trial Management System
CYP	cytochrome P450
CYP2D6	cytochrome P450 2D6
DCP	dyskinesia in cerebral palsy
ECG	Electrocardiogram/Electrocardiography
ESRS	Extrapyramidal Symptom Rating Scale (subscales I and II)
ESS	Epworth Sleepiness Scale (for children and adolescents)
ET	early termination
HR	heart rate
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
ITT	Intent-to-Treat
MD-CRS	Movement Disorder-Childhood Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
n	number
NDA	New Drug Application

Abbreviation	Term
PEDI-CAT	Pediatric Evaluation Disability Inventory-Computer Adapted Test
PR	Time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram
QRS	Graphical deflections corresponding to ventricular depolarization in a typical electrocardiogram
QTc	QT corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	Time between the start of one R wave and the start of the next R wave in the ECG
SD	Standard Deviation
SE	Standard Error
SOC	system organ class
SOP	standard operating procedure
UHDRS-TMC	Unified Huntington's Disease Rating Scale -Total Maximal Chorea
UHDRS-TMD	Unified Huntington's Disease Rating Scale -Total Maximal Dystonia
UHDRS-TMS	Unified Huntington's Disease Rating Scale - Total Motor Score
WHO	World Health Organization
α-HTBZ	alpha-dihydrotetrabenazine
β-HCG	beta-human chorionic gonadotropin
β-HTBZ	beta-dihydrotetrabenazine

INTRODUCTION

This Statistical Analysis Plan describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. Study TV50717-CNS-30081, An Open-Label, Long-Term Safety, Tolerability, and Efficacy Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy (CP) in Children and Adolescents, and was written in accordance with SOP GSD-SOP-702 (Statistical Analysis Plan).

The reader of this Statistical Analysis Plan 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 Statistical Analysis Plan 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 Statistical Analysis Plan may contain more details regarding these particular points of interest, or other types of analyses (e.g. other endpoints).When differences exist in descriptions or explanations provided in the study protocol and this Statistical Analysis Plan, the Statistical Analysis Plan prevails; the differences will be explained in the Clinical Study Report (CSR).

1. STUDY OBJECTIVES

1.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are presented below in Table 1.

Table 1: Primary and Secondary Study Objectives and Endpoints

Objectives	Measures/Endpoints
The **primary objective** of this study is to evaluate the safety and tolerability of long-term therapy with TEV-50717 in children and adolescents with dyskinesia in cerebral palsy (DCP).	The safety measures/endpoints are as follows: • adverse events • vital signs • children's C-SSRS • ECG parameters • clinical laboratory parameters (hematology, serum chemistry, and urinalysis) • ESRS (subscales I and II) • CBCL • ESS
A **secondary objective** of this study is to evaluate the efficacy of long-term therapy with TEV-50717 in reducing the severity of DCP.	The efficacy measures/endpoints are as follows: • MD-CRS part I total score (centrally read) • MD-CRS part II total score (centrally read) • MD-CRS part I total score (physician rated) • MD-CRS part II total score (physician rated) • MD-CRS Global Index (calculated from MD-CRS parts I and II total scores) • CaGI-I (global, caregiver rated) • CGI-I (global, physician rated) • CGI-S (global, physician rated) • PEDI-CAT (ADL, caregiver completed, content-balanced version) • UHDRS-TMC (centrally read) • UHDRS-TMD (centrally read) • UHDRS-TMS (physician rated)

Objectives	Measures/Endpoints
	• UHDRS-TMC (physician rated) • UHDRS-TMD (physician rated) • COPM (physician rated)

CaGI-I=Caregiver Global Impression of Improvement; CBCL=Child Behavior Checklist (for ages 6 to 18); CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; COPM=Canadian Occupational Performance Measure; C-SSRS=Columbia-Suicide Severity Rating Scale; DCP=dyskinesia in cerebral palsy; ECG=electrocardiogram; ESRS=Extrapyramidal Symptom Rating Scale (subscales I and II); ESS=Epworth Sleepiness Scale (for children and adolescents); MD-CRS=Movement Disorder-Childhood Rating Scale; PEDI-CAT=Pediatric Evaluation Disability Inventory-Computer Adapted Test; ADL=activities of daily living; UHDRS-TMC=Unified Huntington's Disease Rating Scale-Total Maximal Chorea; UHDRS-TMD=Unified Huntington's Disease Rating Scale-Total Maximal Dystonia; UHDRS-TMS=Unified Huntington's Disease Rating Scale-Total Motor Score.

2. STUDY DESIGN

2.1. General Design

This is a 55-week, open-label, single-arm study in which patients who have successfully completed the parent study (Study TV50717-CNS-30080) may be eligible to enroll in this study after they complete a 1-week washout period and the final evaluation at week 16. For patients rolling over from Study TV50717-CNS-30080, the week 16 visit may be the day 1 visit for Study TV50717-CNS-30081. If the patient does not wish to enroll in Study TV50717-CNS-30081 at that visit, or for any other reason, the patient can enroll up to 4 weeks following the week 15 visit of Study TV50717-CNS-30080. The end of study TV50717-CNS-30081 is defined as the date of the week 55 follow-up telephone contact of the last participant.

This study will include children and adolescents between 6 and 18 years of age at the time when they enrolled in the parent study (Study TV50717-CNS-30080). Informed consent/assent, as appropriate, based on the patient's age and condition, will be obtained from the patient/parent(s)/legally acceptable representative and caregiver (as applicable) at baseline/day 1 or screening visit (whichever comes first), and before any study procedures are performed.

Patients can either enroll in the study at the week 16 visit of Study TV50717-CNS-30080 or up to 6 months following the week 15 visit of Study TV50717-CNS-30080. The time when the patient enrolls (baseline/day 1) in this study will determine the assessments that will need to be performed at the initial visit for the study. Detailed descriptions of each assessment are provided in Table 2, Figure 2 and Section 4.2.

Titration period (7 weeks): All patients will undergo TEV-50717 dose titration in this study in order to maintain the blind of the parent Study TV50717-CNS-30080. Patients will receive 6 mg of TEV-50717. This dose will be administered in the morning on days 2 and 3, followed by evening administration starting on day 3 for the remainder of the week (if body weight is ≥40 kg/88 lbs). TEV-50717 daily doses of 12 mg and higher will be administered as 2 divided equal doses, approximately 8 to 10 hours apart during the day. A minimum of 6 hours should elapse between doses.

The titration scheme and maximum dose will be determined by body weight at day 1 and cytochrome P450 2D6 (CYP2D6) impairment status. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor. Patients who are CYP2D6 impaired will have a dose cap in the open-label study. Safety evaluations during the titration period include assessment of vital signs, monitoring for adverse events and concomitant medications, 12-lead electrocardiograms (ECG)s, identifying patients at risk for suicide, assessment of drug-induced parkinsonism according to the Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II, assessment of change in behavior according to the Child Behavior Checklist (CBCL) questionnaire, and assessment of sedation according to the Epworth Sleepiness Scale (ESS) questionnaire.

In-person (in-clinic) study visits will be scheduled at weeks 3 and 7, and telephone contacts (with non-recording live video) will be scheduled for weeks 1, 2, 4, 5, and 6 in order to assess dyskinesia and adverse events.

Maintenance period (46 weeks): At the end of the titration period (week 7), the patient's initial dose for the maintenance period (up to week 53) will be established. Dose adjustments of TEV-50717 (upward or downward) may be made during the maintenance period, if necessary, based on efficacy, safety, and/or tolerability considerations but not more often than every 5 days and only in increments of 6 mg up to the maximum allowed dose (see Table 6 and Table 7).

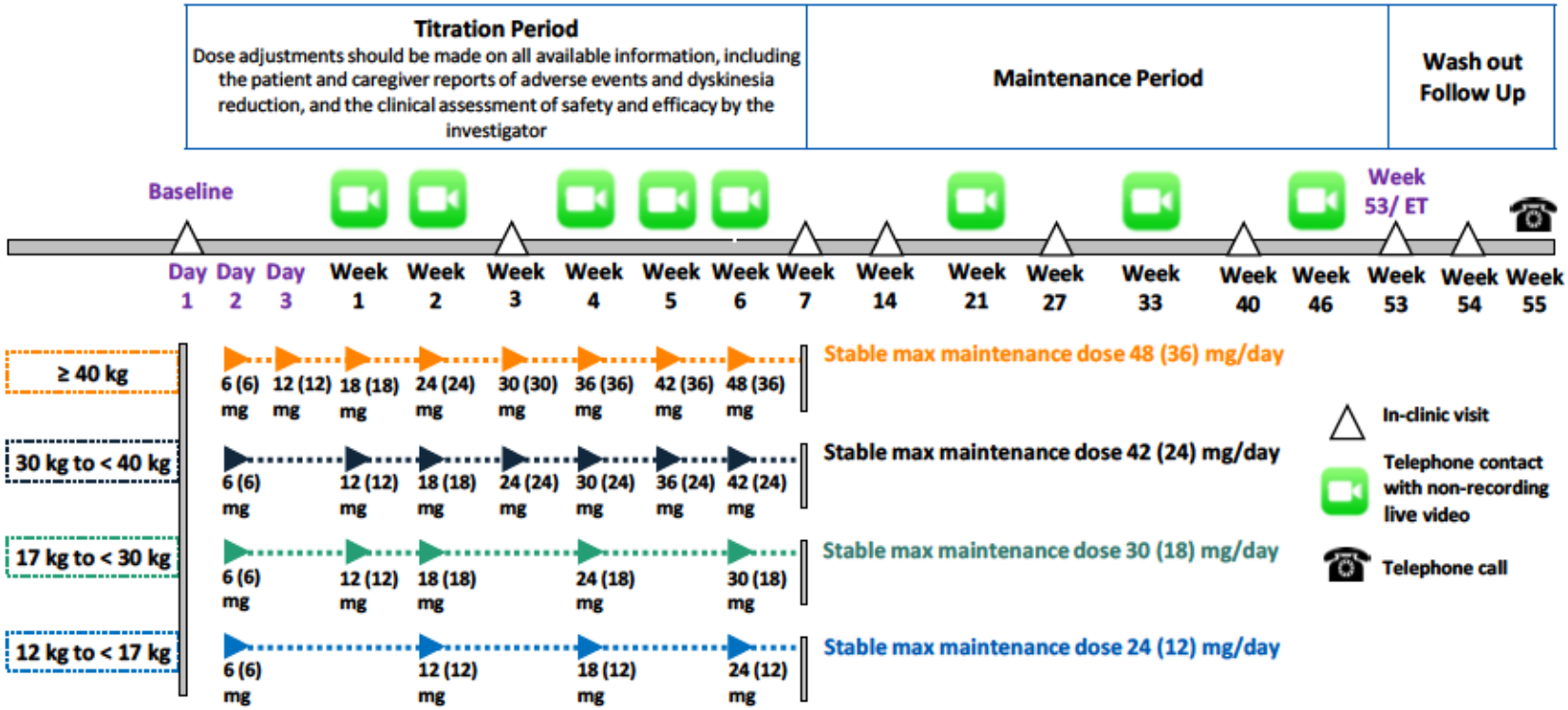
During the maintenance period, in-person (in-clinic) study visits will be scheduled at weeks 14, 27, 40, and 53 for assessments of safety and efficacy, and telephone contacts (with non-recording live video) will be scheduled for weeks 21, 33, and 46 in order to assess adverse events and dyskinesia. At week 53/early termination (ET), patients will undergo a complete evaluation.

Washout and follow-up period: All patients should continue their usual treatment regimen up to week 53 visit (ie, the last dose can be administered until visit completion, if applicable). No dosing will be given after the week 53 visit. All patients will discontinue TEV-50717 at the week 53 visit and will return 1 week later (week 54) for evaluation of safety. Patients will have a follow-up telephone contact (no live video streaming) for safety evaluation 1 week after the end of the washout period (2 weeks after their last dose of TEV-50717) (week 55).

Study procedures and assessments with their time points are presented for screening and/or day 1 in Table 2 and for the titration, maintenance, and follow-up periods in Table 3. The study schematic diagram is presented in Figure 1. A flow chart for patient screening and day 1 visit assessments is presented in Figure 2.

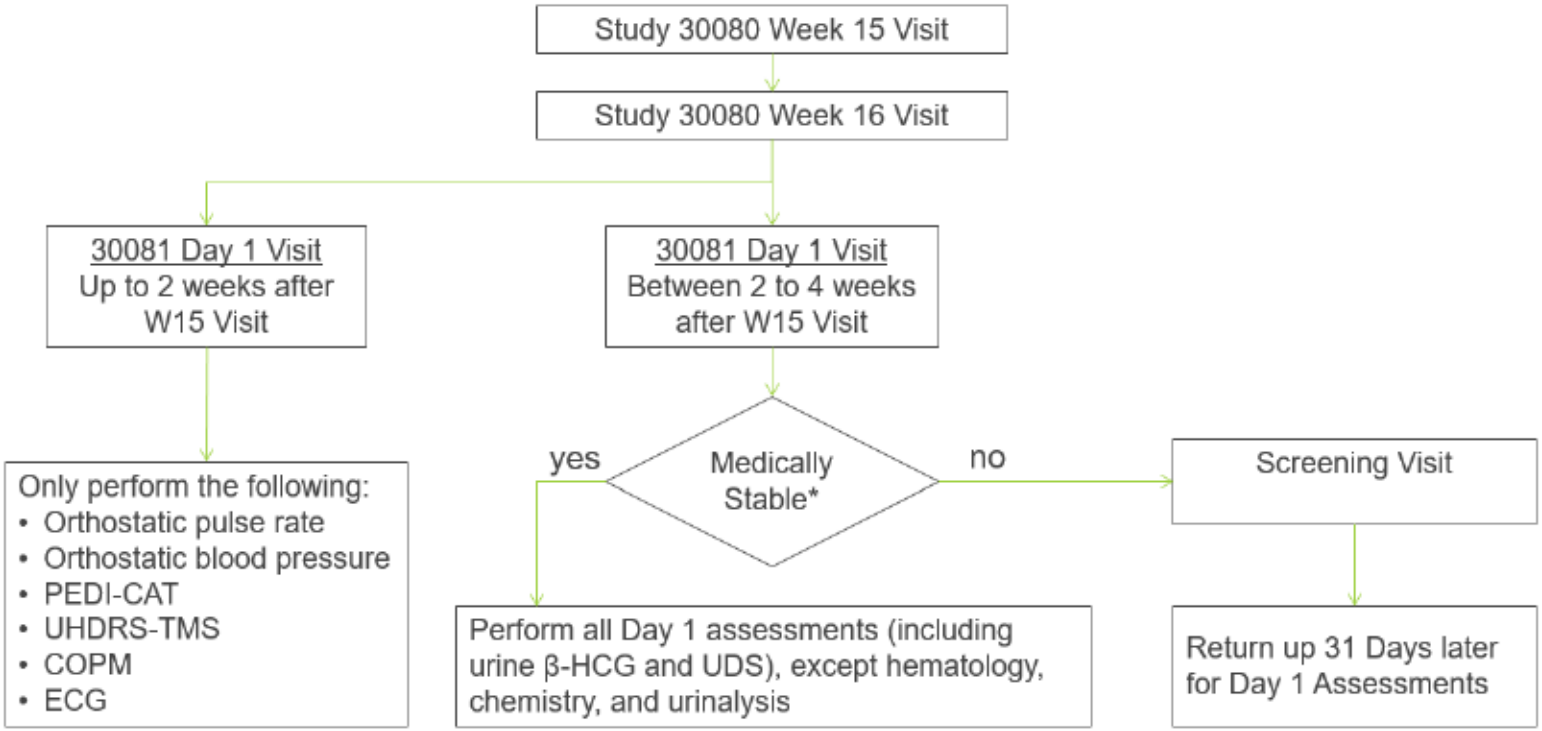
For coronavirus disease 2019 (COVID-19) updates, refer to protocol Appendix M.

Figure 1: Overall Study Schematic Diagram



AE=adverse event; CGI-I=Clinical Global Impression of Improvement; CYP2D6=cytochrome P450 2D6; D=day; ET=early termination; max=maximum; Wk=week.
Note: If a patient is CYP2D6-impaired, the dose administered is indicated in parentheses. The dose of TEV-50717 should be increased until any of the following events occur: clinically meaningful reduction in dyskinesia (ie, CGI-I) as determined by the investigator, clinically significant AE, or the maximum allowable dose is reached. The maintenance period starts at week 7; however, study procedures and assessments are conducted between weeks 14 and 53/ET.

Figure 2: Flow Chart for Patient Screening and Day 1 Visit Assessments



[a] Defined as any clinically significant change since the W15 visit of Study TV50717-CNS-30080 in health, concomitant medications, clinical assessments, laboratories, ECGs, or non-medical interventions.
ECG=electrocardiogram; W15=week 15.

2.2. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented for screening and/or day 1 in Table 2 and for the titration, maintenance, and follow-up periods in Table 3. During a visit, study procedures and assessments should be performed in the order specified in the study manual.

Detail descriptions of each assessment are provided in Section 6 (efficacy assessments) and Section 8 (safety assessments).

For COVID-19 updates, refer to protocol Appendix M.

Table 2: Study Procedures and Assessments – Screening and/or Day 1

	Day 1 **Between 1 and <2 weeks after Study TV50717-CNS-30080 week 15 visit[a]**	**Day 1** **Between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit with no clinically significant changes[b]**	**Day 1** **Between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit and with clinically significant changes[b]**	
Study day	**Day 1/BL**	**Day 1/BL**	**Screening**	**Day 1/BL (within 31 days from screening)**
In-clinic visit	X	X	X	X
Informed consent/assent[c]	X	X	X	
Eligibility criteria	X	X	X	X
Medical history and psychiatric history	X	X	X	
Demographics	[X]	X	X	
Vital signs and weight[d,e]	[X][f]	X[e]	X[e]	X[e]
Physical examination	[X]	X	X	X
Neurological examination	[X]	X	X	X
Height	[X]	X	X	
12-lead ECG[g]	X	X	X	
Chemistry/hematology/ urinalysis	[X][h]	[X][h]	X	
Urine drug screen	[X][h]	[X][h]	X	
β-HCG test	X[i]	X[j]	X[k]	X[j]
MD-CRS part I (centrally read)	X	X		X
MD-CRS part II (centrally read)	X	X		X
MD-CRS part I (physician rated, with video recording)[l]	X	X		X

	Day 1 **Between 1 and <2 weeks after Study TV50717-CNS-30080 week 15 visit[a]**	**Day 1** **Between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit with no clinically significant changes[b]**	**Day 1** **Between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit and with clinically significant changes[b]**	
Study day	**Day 1/BL**	**Day 1/BL**	**Screening**	**Day 1/BL (within 31 days from screening)**
MD-CRS part II (physician rated, with video recording)[l]	X	X		X
CGI-S (global, physician rated)	X	X		X
PEDI-CAT (ADL, caregiver completed, content-balanced version)	X	X		X
UHDRS-TMC (centrally read)	X	X		X
UHDRS-TMD (centrally read)	X	X		X
UHDRS-TMS (physician rated)	X	X		X
UHDRS-TMC (physician rated)	X	X		X
UHDRS-TMD (physician rated)	X	X		X
COPM (physician rated)	X	X		X
C-SSRS (children's baseline/screening)[m]	X[n]	X[n]	X[n]	X[n]
C-SSRS (children's since last visit)[m]	X	X	X	X
ESRS (subscales I and II)	X	X		X
CBCL	X[o]	X[o]	X[o]	X[p]
ESS	X	X	X	X
Assess adverse events	X	X	X	X
Concomitant medications[q]	X	X	X	X
Dispense TEV-50717[r]	X	X		X
Contact IWRS	X	X		X

[a] Assessments indicated in brackets by "[X]" are representative of data carried over from week 15/16 of Study TV50717-CNS-30080, whichever is more current. Any scales/questionnaires administered at the week 16 visit for Study TV50717-CNS-30080 do not need to be repeated if the day 1 visit of Study TV50717-CNS-30081 is the same day as the week 16 visit Study TV50717-CNS-30080.

[b] Defined as clinically significant change since the week 15 visit of Study TV50717-CNS-30080 in health, concomitant medications, clinical assessments, laboratories, ECGs, or non-medical interventions, in the judgment of the investigator.

[c] Informed consent/assent, as appropriate, based on the patient's age, will be obtained from the patient/parent/legally acceptable representative and caregiver (as applicable) at baseline/day 1 or screening visit (whichever comes first), and before any study procedures are performed. The informed consent/assent process can begin within 4 weeks before possible participation in the open-label study to allow patients adequate time to engage and ask questions.

[d] Orthostatic BP and pulse will be measured after the patient is in a standing position for at least 3 minutes (for patients who are able to stand).

[e] Weight must be measured with shoes and outerwear off. Before pulse and BP are measured, the patient must be in a supine or semi-erect/seated position and resting for at least 3 minutes (the same position and arm/leg should be used each time vital signs are measured for a given patient).

[f] Orthostatic blood pressure and orthostatic pulse rate will be measured at day 1. Weight measurements will be carried over from the week 16 visit of Study TV50717-CNS-30080. All other vital sign assessments (respiratory rate and body temperature) will be carried over from the week 16 visit of Study TV50717-CNS-30080, if the day 1 visit in Study TV50717-CNS-30081 is on the same day as the week 16 visit of Study TV50717-CNS-30080. Otherwise, these vital sign assessments will be performed at day 1.

[g] All ECGs will be performed after at least a 5-minute rest in a supine or semi-supine position.

[h] These data will be taken from the week 15 visit of Study TV50717-CNS-30080, unless more current data from the week 16 visit are available.

[i] For females who are postmenarchal or ≥12 years of age. If the day 1 visit in Study TV50717-CNS-30081 is on the same day as the week 16 visit of Study TV50717-CNS-30080, the results of β-HCG tests in urine will be carried over from the week 16 visit. Otherwise, the β HCG tests in urine will be administered at day 1.

[j] For females who are postmenarchal or ≥12 years of age, a β-HCG test in urine will be administered. A patient with a positive β-HCG test in urine cannot be enrolled until a β-HCG test in serum has been performed and is negative.

[k] For females who are postmenarchal or ≥12 years of age, a β-HCG test in serum will be administered.

[l] MD-CRS parts I and II assessments are done locally at the investigational center by the investigator, video recorded. In certain instances, based on the experience of the rater, certain non-physicians may be approved to rate the MD-CRS.

[m] Children 13 years of age and under must be interviewed in conjunction with the caregiver. For children over 13 years of age, caregiver involvement is strongly encouraged. Questions should be directed to the child, but the caregiver should be encouraged to add relevant information. The children's C-SSRS questionnaire will only be presented to patients aged ≥12 years.

[n] If the patient turned 12 years old during or after Study TV50717-CNS-30080, but before screening or day 1 visit of Study TV50717-CNS-30081, whichever comes first, the C-SSRS baseline/screening scale is administered. If the patient turns 12 years old during the study, C-SSRS baseline/screening will be completed as the initial assessment and the C-SSRS Since Last Visit will be completed as per Table 5.

[o] A full CBCL assessment (Competence Scale [Parts I to VII] and a Syndrome Scale [behavioral items]) will be performed.

[p] Only the CBCL Syndrome Scale (behavioral items) will be performed.

[q] Patients and/or caregivers will be instructed during the course of the study to notify the investigator if any new medication is prescribed or if there is any change in current medications, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator.

[r] TEV-50717 will be dispensed once all procedures and eligibility-related assessments are completed and patient eligibility is confirmed.

ADL=activities of daily living; β-HCG=beta-human chorionic gonadotropin; BL=baseline visit; BP=blood pressure; CBCL=Child Behavior Checklist (for ages 6 to 18 years); CGI-S=Clinical Global Impression of Severity; COPM=Canadian Occupational Performance Measure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ESRS=Extrapyramidal Symptom Rating Scale (subscales I and II); ESS=Epworth Sleepiness Scale (for children and adolescents); IWRS=Interactive Web Response Systems; MD-CRS=Movement Disorder-Childhood Rating Scale; PEDI-CAT=Pediatric Evaluation Disability Inventory-Computer Adapted Test; UHDRS-TMC=Unified Huntington's Disease Rating Scale-Total Maximal Chorea; UHDRS-TMD=Unified Huntington's Disease Rating Scale-Total Maximal Dystonia; UHDRS-TMS=Unified Huntington's Disease Rating Scale-Total Motor Score; W15=week 15; W16=week 16.

Note: It is recommended that the same order of administration/completion of the scales be kept per patient throughout the study, as best as possible (refer to the Study TV50717-CNS-30081 Open-RECLAIM-DCP: Order of scales administration/completion document). The investigator should review the scales in a timely manner for any potential reporting of adverse events and document this review accordingly.

Table 3: Study Procedures and Assessments – Titration, Maintenance, and Follow-up Periods

	Titration							Maintenance[a]							Follow-up		U
Study week[b]	1	2	3	4	5	6	7	14	21	27	33	40	46	53/ ET[c]	54	55[d]	
Study day	7	14	21	28	35	42	49	98	147	189	231	280	322	371	378	385	
Visit window (days)	+1 day from Day 1/BL	±1 day from Day 1/BL	±3 days from Day 1/BL and ≥5 days from last dose change					±7 days from Day 1/BL and ≥5 days from last dose change							±2 days from week 53	±2 days from week 54	
In-clinic visit			X				X	X		X		X		X	X		X
Telephone contact[e]	X	X		X	X	X			X		X		X			X	X[f]
Evaluate/adjust TEV-50717[g]	X	X	X	X	X	X	X	X[h]	X	X	X	X	X				X
Vital signs and weight[i]			X				X	X		X		X		X	X		X
Physical examination										X				X			X[f]
Neurological examination														X	X		X[f]
Height										X				X			X
12-Lead ECG[j]			X				X	X		X		X		X	X		X[f]
Chemistry/hematology/urinalysis			X				X	X		X		X		X	X		X[f]
Urine drug screen										X				X			X[f]
β-HCG test[k]								X		X		X		X	X		X[f]
MD-CRS part I (centrally read)[l]										X				X	X		
MD-CRS part II (centrally read) [l]										X				X	X		
MD-CRS part I (physician rated with video recording) [m]								X		X		X		X	X		
MD-CRS part II (physician rated with video recording)[m]								X		X		X		X	X		
CaGI-I (global, caregiver rated) [n]								X		X		X		X	X		
CGI-I (global, physician rated) [o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-S (global, physician rated)[o]								X		X		X		X	X		

	Titration							Maintenance[a]							Follow-up		U
Study week[b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**21**	**27**	**33**	**40**	**46**	**53/ ET[c]**	**54**	**55[d]**	
Study day	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**98**	**147**	**189**	**231**	**280**	**322**	**371**	**378**	**385**	
Visit window (days)	**+1 day from Day 1/BL**	**±1 day from Day 1/BL**	**±3 days from Day 1/BL and ≥5 days from last dose change**					**±7 days from Day 1/BL and ≥5 days from last dose change**							**±2 days from week 53**	**±2 days from week 54**	
PEDI-CAT (ADL, caregiver completed, content-balanced version)										X				X			
UHDRS-TMC (centrally read)[l]										X				X	X		
UHDRS-TMD (centrally read)[l]										X				X	X		
UHDRS-TMS (physician rated)								X		X		X		X			
UHDRS-TMC (physician rated)								X		X		X		X			
UHDRS-TMD (physician rated)								X		X		X		X			
COPM (physician rated)										X				X			
C-SSRS (children's since last visit)[o]			X				X	X		X		X		X	X		X[f]
ESRS (subscales I and II)			X				X	X		X		X		X	X		X[f]
CBCL[p]			X				X	X		X		X		X	X		X[f]
ESS			X				X	X		X		X		X	X		X[f]
Dispense TEV-50717[q]			X[r]				X	X		X		X					X[f]
Collect TEV-50717			X[r]				X	X		X		X		X			X[f]
Assess TEV-50717 accountability/ compliance/supply[s]	X	X	X[r]	X	X	X	X	X	X	X	X	X	X	X			X[f]
Assess adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample collection for TEV-50717 concentration[t]														X			X

	Titration							Maintenance[a]							Follow-up		U
Study week[b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**21**	**27**	**33**	**40**	**46**	**53/ ET[c]**	**54**	**55[d]**	
Study day	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**98**	**147**	**189**	**231**	**280**	**322**	**371**	**378**	**385**	
Visit window (days)	**+1 day from Day 1/BL**	**±1 day from Day 1/BL**	**±3 days from Day 1/BL and ≥5 days from last dose change**					**±7 days from Day 1/BL and ≥5 days from last dose change**							**±2 days from week 53**	**±2 days from week 54**	
Concomitant medications[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IWRS			X				X	X		X		X		X			X

[a] The maintenance period starts at week 8; however, study procedures and assessments are conducted between weeks 14 and 53/ET.

[b] Assessment to occur at the end of study week, unless stated otherwise.

[c] For patients who withdraw prematurely, an ET visit should be conducted as soon as possible after the last dose of TEV-50717. All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after their last dose of TEV-50717; evaluations will be as described for the week 55 visit.

[d] This visit is a telephone contact for safety evaluation.

[e] Telephone contacts at weeks 1, 2, 4, 5, 6, 21, 33, and 46 will be conducted with non-recording live video. Telephone contact at week 55 is a phone contact only (ie, no live video streaming).

[f] Assessment to be completed at investigator's discretion.

[g] Dose increases may not occur more frequently than every 5 days, except for patients ≥40 kg. For patients ≥40 kg, the first dose increase should be performed in an interval less than 5 days, only once, on day 3.

[h] Patients will continue to receive their maintenance dose from week 8 to week 53. Dose reductions or suspensions for adverse events are allowed.

[i] Weight must be measured with shoes and outerwear off. Before pulse and BP are measured, the patient must be in a supine or semi-erect/seated position and resting for at least 3 minutes (the same position and arm/leg should be used each time vital signs are measured for a given patient). Orthostatic BP and pulse will be measured after the patient is in a standing position for at least 3 minutes (for patients who are able to stand) and should be measured at W14 and W53/ET.

[j] All ECGs will be performed after at least 5-minute rest in a supine or semi-supine position.

[k] For females who are postmenarchal or ≥12 years of age, a urine pregnancy test will be administered at weeks 14, 27, 40, and 54/follow-up visit while a serum pregnancy test will be administered at week 53/ET, and if clinically indicated.

[l] Central reading is based on the video recordings, and is done in a blinded manner

[m] MD-CRS parts I and II assessments are done locally at the investigational center by the investigator, video recorded. In certain instances, based on the experience of the rater, certain non-physicians may be approved to rate the MD-CRS.

[n] CaGI-I is to be assessed before all other investigator-rated scales during visits where CaGI-I is collected.

[o] Children 13 years of age and under must be interviewed in conjunction with the caregiver. For children over 13 years of age, caregiver involvement is strongly encouraged. Questions should be directed to the child, but the caregiver should be encouraged to add relevant information. The children's C-SSRS

questionnaire will only be presented to patients aged ≥12 years. Children who turn 12 years old during the study will be administered C-SSRS (baseline/screening) as initial assessment during the study.

[p] A full CBCL assessment (Competence Scale [Parts I to VII] and a Syndrome Scale [behavioral items]) will be performed at week 53/ET. The Syndrome Scale part of the CBCL assessment will be performed at weeks 3, 7, 14, 27, 40, 53/ET visit, and 54/follow-up visits.

[q] For any dose adjustment, the investigator or designee should confirm that patients have the bottle that contains the appropriate tablet strength and quantity to complete the recommended daily regimen.

[r] During the week 3 visit, the investigator (or designee) will make sure the patient receives the evening dose to complete the week 3 dosing for that day. Refer to the pharmacy manual for further details.

[s] Study drug accountability will be assessed during in-clinic visits only. A check for compliance with TEV-50717 intake will be performed during each in-clinic visit and telephone contact after TEV-50717 has been dispensed.

[t] Patients experiencing an adverse event leading to discontinuation of TEV-50717, or experiencing any other adverse event, should have a single blood sample collected for the measurement of TEV-50717, α-HTBZ and β HTBZ concentrations, if possible. This should be done (at the discretion of the investigator) as soon as possible after the onset of the ongoing adverse event and within 48 hours after the last dose intake in the case of TEV 50717 discontinuation. To permit the assessment of a potential relationship of the adverse event and plasma concentration, an estimate of the date and time of the last dose intake of study drug should be recorded along with the date and time of the sample collection. If the estimate of the dose intake cannot be established within a 2-hour window, then a blood sample should not be obtained.

[u] Patients and/or caregivers will be instructed during the course of the study to notify the investigator if any new medication is prescribed, or if there is any change in current medication, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator.

ADL=activities of daily living; β-HCG=beta human chorionic gonadotropin; BL=baseline visit; BP=blood pressure; CaGI-I=Caregiver Global Impression of Improvement; CBCL=Child Behavior Checklist (for ages 6 to 18 years); CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; COPM=Canadian Occupational Performance Measure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ESRS=Extrapyramidal Symptom Rating Scale (subscales I and II); ESS=Epworth Sleepiness Scale (for children and adolescents); ET=early termination visit; HTBZ= dihydrotetrabenazine (active metabolite); IWRS=Interactive Web Response Systems; MD-CRS=Movement Disorder-Childhood Rating Scale; PEDI-CAT=Pediatric Evaluation Disability Inventory-Computer Adapted Test; U=unscheduled visit; UHDRS-TMC=Unified Huntington's Disease Rating Scale-Total Maximal Chorea; UHDRS-TMD=Unified Huntington's Disease Rating Scale-Total Maximal Dystonia; UHDRS-TMS=Unified Huntington's Disease Rating Scale-Total Motor Score.

Note: It is recommended that the same order of administration/completion of the scales be kept per patient throughout the study, as best as possible (refer to the Study TV50717-CNS-30081 Open-RECLAIM-DCP: Order of scales administration/completion document). The investigator should review the scales in a timely manner for any potential reporting of adverse events and document this review accordingly.

2.3. Randomization and Blinding

This is an open-label, single-arm study, and there is no blinding.

2.4. Data Monitoring Committee

There will be an Independent Data Monitoring Committee (iDMC) in this study. During the conduct of this study, an iDMC will review accumulating safety data on a regular basis to ensure the continuing safety of the study patients and to review any study conduct issues.

2.5. Sample Size and Power Considerations

This study is open-label and safety oriented in nature; therefore, no formal hypothesis testing is planned. The sample size for this study is not based on statistical considerations; hence, only descriptive statistics will be presented.

Based on the number of patients in the parent study (Study TEV50717-CNS-30080) approximately 45 patients who completed the parent study may enroll in this study.

2.6. Sequence of Planned Analyses

2.6.1. Planned Interim Analyses

There is no planned interim analysis of this study. Intermediate analysis may be performed for submission of a New Drug Application (NDA) or other purposes.

2.6.2. Final Analyses and Reporting

All analyses identified in this Statistical Analysis Plan will be performed after the end of study as defined in the study protocol.

This final version of the Statistical Analysis Plan and any corresponding amendments will be approved before database lock, in accordance to SOP GBP_RD_702 (Statistical Analysis Plan).

3. ANALYSIS SETS

3.1. Intent-to-Treat Analysis Set

The intent to treat (ITT) analysis set will include all enrolled patients, regardless of whether or not a patient took any TEV-50717. A patient is considered enrolled according to the status in the database.

Both safety and efficacy analyses will be based on the ITT analysis set.

3.2. Additional Analysis Set

No additional analysis set is planned.

In case of a patient who enrolled but without taking any investigational medicinal product (IMP), a safety analysis set will be considered as an exploratory analysis set for safety assessments. This safety analysis set will include all enrolled patients who receive at least 1 dose of IMP.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include number (n), mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. Mean, SD and SE will not be presented if the number of patients in the analysis is less than 5 ($n < 5$).

Descriptive statistics for categorical variables include patient counts and percentages. Missing category will be displayed as appropriate.

4.2. Specification of Baseline Values

Generally, the baseline value is the last observed data before the first dose of IMP, unless otherwise noted. If the baseline assessments occur on the same day as the first dose of IMP, it is assumed that the patients follow study procedure and those baseline assessments will be used.

The baseline assessments that will need to be performed at the initial visit for the study will be determined at the time when the patient enrolls (baseline/day 1).

Day 1: Between 1 and <2 weeks after Study TV50717-CNS-30080 week 15 visit:

To reduce patient burden and not collect duplicate information, after obtaining appropriate informed consent/assent, relevant data collected in Study TV50717-CNS-30080 will be used to provide corresponding data in this open-label study baseline/day 1 visit.

Day 1 assessments for Study TV50717-CNS-30081 that are identical to Study TV50717-CNS-30080 week 15/week 16 visit assessments, whichever is most current, **do not** need to be repeated, except for orthostatic pulse rate and blood pressure, ECG, beta-human chorionic gonadotropin (β-HCG) tests in urine, the site-administered scales, and the patient/caregiver-completed questionnaires, which need to be repeated at day 1.

Any scales/questionnaires administered at the week 16 visit for Study TV50717-CNS-30080 do not need to be repeated if the day 1 visit of Study TV50717-CNS-30081 is the same day as the week 16 visit Study TV50717-CNS-30080. See protocol Section 3 for addition details for day 1 baseline assessments.

Day 1: Between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit:

If, in the judgment of the investigator, the patient has ***not*** had any clinically significant change since the week 15 visit of Study TV50717-CNS-30080 in health, concomitant medications, clinical assessments, laboratories, ECGs, or non-medical interventions, the patient will undergo all day 1 assessments outlined in Table 2, except hematology, chemistry, and urinalysis laboratories and urine drug screen, which can be carried over from Study TV50717-CNS-30080 week 15 or week 16 visit, whichever is more current.

If, in the judgment of the investigator, the patient has had a clinically significant change since the week 15 visit of Study TV50717-CNS-30080 in health, concomitant medications, clinical assessments, laboratories, ECGs, or non-medical interventions, the patient will undergo all screening procedures outlined in Table 2. Patients who remain eligible for participation in the study will be asked to return for day 1 assessments.

Study drug will be dispensed at day 1 once all procedures and investigator-related assessments are completed and patient eligibility is confirmed.

4.3. Handling Withdrawals and Missing Data

For most variables, only observed data from the patients will be used in the statistical analyses, ie, there is no plan to impute missing data for these variables, unless otherwise specified.

Rules for handling missing items in efficacy and safety rating scales/questionnaire are presented in Section 6.2.2 and Section 8.

4.4. Study Days and Visits

Study days will be numbered relative to the baseline visit date. Day 1 is defined as the date of the baseline visit, and the first dose of the IMP will be taken the next morning (day 2). Days will be numbered relative to baseline (ie, ..., –2, –1, 1, 2, ...; day –1 being the day before the baseline visit).

For efficacy and safety by-visit analyses, data collected at post-baseline scheduled visits will be included using their scheduled visit.

Data collected at early termination and unscheduled visits will be included and assigned to a visit window as described below.

Table 4: Visit Windows for Early Termination Visit for Efficacy Assessments

Assessment[a]	Study Day Window	Scheduled Day	Scheduled Visit/Week
MD-CRS, CaGI-I, CGI-S	Day 2 - 143	Day 98	Week 14
	Day 144 - 234	Day 189	Week 27
	Day 235 - 325	Day 280	Week 40
	Day 326 - 374	Day 371	Week 53
	≥Day 375	Day 378	Week 54
UHDRS-TMS, UHDRS-TMC, UHDRS-TMD	Day 2 - 143	Day 98	Week 14
	Day 144 - 234	Day 189	Week 27
	Day 235 - 325	Day 280	Week 40
	≥Day 326	Day 371	Week 53
PEDI-CAT, COPM	Day 2 - 280	Day 189	Week 27
	≥Day 281	Day 371	Week 53

Assessment[a]	Study Day Window	Scheduled Day	Scheduled Visit/Week
CGI-I	Day 2 – 10	Day 7	Week 1
	Day 11 – 17	Day 14	Week 2
	Day 18 – 24	Day 21	Week 3
	Day 25 – 31	Day 28	Week 4
	Day 32 – 38	Day 35	Week 5
	Day 39 – 45	Day 42	Week 6
	Day 46 – 73	Day 49	Week 7
	Day 74 – 122	Day 98	Week 14
	Day 123 - 168	Day 147	Week 21
	Day 169 – 210	Day 189	Week 27
	Day 211 – 255	Day 231	Week 33
	Day 256 – 301	Day 280	Week 40
	Day 302 – 346	Day 322	Week 46
	Day 347 – 374	Day 371	Week 53
	Day 375 – 381	Day 378	Week 54
	≥Day 382	Day 385	Week 55

[a] MD-CRS=Movement Disorder-Childhood Rating Scale; CaGI-I=Caregiver Global Impression of Improvement; CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; UHDRS-TMS=Unified Huntington's Disease Rating Scale–Total Motor Score; UHDRS-TMC=Unified Huntington's Disease Rating Scale–Total Maximal Chorea; UHDRS-TMD=Unified Huntington's Disease Rating Scale–Total Maximal Dystonia; PEDI-CAT=Pediatric Evaluation Disability Inventory-Computer Adapted Test; COPM=Canadian Occupational Performance Measure;

Table 5: Visit Windows for Early Termination Visit for Safety Assessments

Assessment[a]	Study Day Window	Scheduled Day	Scheduled Visit/Week
Vital signs and weight, 12-Lead ECG, C-SSRS, ESRS, CBCL-Syndrome Scale, ESS, Chemistry/hematology/ urinalysis	Day 2 – 35	Day 21	Week 3
	Day 36 – 73	Day 49	Week 7
	Day 74 – 143	Day 98	Week 14
	Day 144 – 234	Day 189	Week 27
	Day 235 – 325	Day 280	Week 40
	Day 326 – 374	Day 371	Week 53
	≥Day 375	Day 378	Week 54
Physical examination, Height	Day 2 – 280	Day 189	Week 27
	≥Day 281	Day 371	Week 53

Assessment[a]	Study Day Window	Scheduled Day	Scheduled Visit/Week
Orthostatic Vital Signs	Day 2 – 234	Day 98	Week 14
	>Day 235	Day 371	Week 53
Neurological examination	Day 2 – 374	Day 371	Week 53
	≥Day 375	Day 378	Week 54
CBCL-full assessment	≥Day 2	Day 371	Week 53

[a] CBCL=Child Behavior Checklist (for ages 6-18); C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ESRS=Extrapyramidal Symptom Rating Scale (subscales I and II); ESS =Epworth Sleepiness Scale (for children and adolescents);

After mapping the data to the analysis visits of unscheduled and early termination visits, the following rules will apply unless other handling is specified for a particular analysis:

- If there is a scheduled visit in the analysis window, the last non-missing scheduled visit will be selected.
- If there is no scheduled visit, but early termination visit, early termination visit will be selected.
- If there are no scheduled or early termination visits, the record closest to the planned assessment day will be selected for analysis.
- If there are no scheduled or early termination visits, and 2 records are equidistant from the scheduled day, then the later record will be selected.
- If a patient has no scheduled record or early termination/unscheduled visits in an analysis window, the patient will be considered missing at that visit.

For these analyses performed by time period, eg, adverse events, the following definitions will be used:

- Titration Period - from the first dose of treatment until the day of the week 7 visit. For patients discontinued before the week 7, the Titration Period is until the later of the last dose of treatment and the early termination visit.
- Maintenance Period - from the day after the week 7 visit until the day of the week 53 visit. If a patient enters the Maintenance Period but discontinues treatment early, the Maintenance Period is until the later of the last dose of treatment and the early termination visit.
- 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.

4.5. Handling Data From Patients who Withdraw and Re-Enter the Study

Patients who terminate early from the study due to emergency circumstances (such as coronavirus disease 2019 [COVID-19]) may be allowed to re-enter the study at a later date.

Patients re-entering the study will redo the entire study from the start.

4.5.1. Baseline Values

In general, baseline values from the re-entered participation will be used. Missing baseline values will be handled in the same method as other non-withdrawal patients.

Results from the original participation of the CYP2D6 impairment status at baseline will be carried over to the repeated participation (re-entered) portion.

4.5.2. Postbaseline Data

For each patient that re-entered the study, only data from the repeated participation will be included in the ITT analysis set. The original participation data will be listed separately and will not be included in any summary tables. In case of a SAE that occurred during the original participation and resolved prior to re-entering, the SAE will be documented in medical history database. Missing postbaseline data will be handled in the same method as other non-withdrawal patients.

5. STUDY POPULATION

5.1. General

The ITT analysis set will be used for all study population summaries unless otherwise specified. Summaries will be presented for all patients.

5.2. Patient Disposition

Data from patients who are enrolled; patients enrolled but not treated; patients in the ITT; patients who complete the treatment period; patients who withdraw from the treatment period; patients who complete the end of study visit, and patients who withdraw from the study will be summarized using descriptive statistics.

Data from patients who withdraw from the treatment period and withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

5.3. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized using descriptive statistics.

Body mass index (BMI) will be computed as:

BMI (kg/m^2) = Weight at baseline (kg)/[Height at screening $(m)^2$]

Normal age and sex-based z-scores and percentiles for BMI will be determined using the World Health Organization (WHO) growth charts. Age and sex-based BMI categories includes: Underweight (< 5 percentile), Normal (≥ 5- < 85 percentile), Overweight (≥ 85 - < 95 percentile), Obese (≥ 95 percentile).

The continuous variables of patient age, weight, height, BMI, BMI WHO adjusted z-scores and percentile, will be summarized using descriptive statistics.

The categorical variables of patient weight group, sex, race, ethnicity, region (United States (US) and non-US), country for non-US, age group (6 to 11 years, 12 to 18 years), CYP2D6 impairment status (Impaired/Not impaired), and BMI categories will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

5.4. Disease Characteristics

Not applicable.

5.5. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term. Patients are counted only once in each preferred term and SOC category. Summaries will be presented for all patients.

5.6. Prior Therapy and Medication

Any prior or concomitant medication a patient has had within 30 days prior to baseline and up to the end of study, including follow up, will be recorded on the case report form (CRF). Generic or trade name, indication, dose, and start and end dates of the administered medication will be recorded. The sponsor will encode all medication according to the WHO drug dictionary.

The incidence of prior therapies and medications will be summarized using descriptive statistics by therapeutic class, preferred base name and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior therapies and medications will include all medications taken and therapies administered before the first day of IMP administration.

5.7. Study Drug Titration

The number and percent of patients at each dose level by weight group and CYP2D6 impairment status during the titration period will be summarized by week. The latest administered dose in each study week will be used.

Reasons for the deviation from the IMP administration will be summarized overall and by period (titration and maintenance).

Descriptive statistics of the maintenance dose (last dose taken in the maintenance period; nominal and as percent of the maximal planned dose for the patient) will be presented.

5.8. Study Drug Compliance

Study drug compliance during the treatment period will be assessed at described in the protocol Section 5.7.

Study drug compliance will be determined by presenting the number of tablets taken as a percentage of the expected number of tablets based on the dose(s) of the patient at the relevant time period (see Table 6 and Table 7; protocol Section 5.1).

Table 6: Dispensing Drug Kits based on Weight Group at Baseline/Day 1 Titration Scheme – Non-Impaired CYP2D6 Metabolizers

Weight Group	12 kg to <17 kg		17 kg to <30 kg		30 kg to <40 kg		≥40 kg	
Study Time Period	Dose (mg/day)	Tablets (mg)	Dose (mg/day)	Tablets (mg)	Dose (mg/day)	Tablets (mg)	Dose (mg/day)	Tablets (mg)
Day 2	6	6	6	6	6	6	6	6
Week 1	6	6	6	6	6	6	12	6, 6
Week 2	6	6	12	6, 6	12	6, 6	18	9, 9
Week 3	12	6, 6	18	9, 9	18	9, 9	24	12, 12
Week 4	12	6, 6	18	9, 9	24	12, 12	30	15, 15
Week 5	18	9, 9	24	12, 12	30	15, 15	36	18, 18
Week 6	18	9, 9	24	12, 12	36	18, 18	42	15, 6 AM 15, 6 PM
Week 7	24	12, 12	30	15, 15	42	15, 6 AM 15, 6 PM	48	12, 12 AM 12, 12 PM

CYP2D6=cytochrome P450 2D6. Dose and tables refer to IMP. Maximal dose according to the titration scheme is presented.

Table 7: Dispensing Drug Kits based on Weight Group at Baseline/Day 1 Titration Scheme – Impaired CYP2D6 Metabolizers

Weight Group	12 kg to <17 kg		17 kg to <30 kg		30 kg to <40 kg		≥40 kg	
Study Time Period	Dose (mg/day)	Tablets (mg)	Dose (mg/day)	Tablets (mg)	Dose (mg/day)	Tablets (mg)	Dose (mg/day)	Tablets (mg)
Day 2	6	6	6	6	6	6	6	6
Week 1	6	6	6	6	6	6	12	6, 6
Week 2	6	6	12	6, 6	12	6, 6	18	9, 9
Week 3	12	6, 6	18	9, 9	18	9, 9	24	12, 12
Week 4	12	6, 6	18	9, 9	24	12, 12	30	15, 15
Week 5	12	6, 6	18	9, 9	24	12, 12	36	18, 18
Week 6	12	6, 6	18	9, 9	24	12, 12	36	9, 9 AM 9, 9 PM
Week 7	12	6, 6	18	9, 9	24	6, 6 AM 6, 6 PM	36	9, 9 AM 9, 9 PM

CYP2D6=cytochrome P450 2D6. Dose and tables refer to IMP. Maximal dose according to the titration scheme is presented.

The number of tablets used is the number of tablets dispensed minus the number of tablets returned. If a patient does not return a pill bottle, it will be assumed that the patient took no IMP from that bottle for the purposes of calculating compliance.

The denominator of "expected number of tablets" will be calculated based on patients' participation in the study (ie, last day of study drug – first day of study drug + 1) and the

expected dose according to the Randomization Trial Supply Management system. Adjustments may be required for the doses split between the morning and the evening dose. Of note, the protocol allows the investigator not to titrate a patient up to the maximal possible dose by weight group and CYP2D6 impairment status; therefore the expected number of tablets will be calculated individually. Moreover, drug suspensions and reductions based on investigator instructions are considered as change in the expected number of tablets and are not considered non-compliance. For patients who complete the study, the last day of study drug used in the denominator calculation will be the last expected dosing day. For early termination patients, the last day of study drug used in the denominator calculation will be the last expected dosing day before termination day.

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.

Treatment compliance (%) will be summarized as continuous data using descriptive statistics. In addition, treatment compliance will be summarized as categorical data using descriptive statistics for the following categories: <80%, 80% to 105%, >105%. Compliance will be presented by visit, by overall in the titration and maintenance periods, and by overall in the treatment period.

An additional assessment of the IMP compliance may be performed while taking into account the patient's dose.

5.9. Study Protocol Deviations

Any protocol deviation (as recorded in the Clinical Trial Management System [CTMS]) that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered an important protocol deviation.

Important protocol deviation will be summarized overall and for each category using descriptive statistics. All protocol deviations will be listed.

6. EFFICACY ANALYSIS

6.1. General

The ITT analysis sets will be used for all efficacy analyses. All efficacy endpoints will be summarized using descriptive statistics.

6.2. Efficacy Endpoints and Analysis

Descriptive statistics for continuous variables include n, mean, SD, SE of the mean, median, minimum, and maximum. Minimum and maximum will have the same number of decimal points as the original data. Mean and median will have 1 more decimal point than the original data. SD and SE will have 2 more decimal points than the original data.

Note, descriptive statistics of change from baseline will utilize day 1 from the present open-label study (Study TEV-50717-30081) or week 16 visit from the parent double-blind study (Study TV50717-CNS-30080).

6.2.1. Efficacy Endpoints

Efficacy endpoints will be assessed in this study as follows:

- MD-CRS part I total score (centrally read)
- MD-CRS part II total score (centrally read)
- MD-CRS part I total score (physician rated)
- MD-CRS part II total score (physician rated)
- MD-CRS Global Index (calculated from MD-CRS parts I and II total scores)
- Caregiver Global Impression of Improvement (CaGI-I) Scale (global, caregiver rated)
- Clinical Global Impression of Improvement (CGI-I) Scale (global, physician rated)
- Clinical Global Impression of Severity (CGI-S) Scale (global, physician rated)
- Pediatric Evaluation Disability Inventory-Computer Adapter Test (PEDI-CAT) (ADL, caregiver completed, content-balanced version)
- Unified Huntington's Disease Rating Scale-Total Maximal Chorea (UHDRS-TMC) (centrally read)
- Unified Huntington's Disease Rating Scale-Total Maximal Dystonia (UHDRS-TMD) (centrally read)
- Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) (physician rated)
- UHDRS-TMC (physician rated)
- UHDRS-TMD (physician rated)
- Canadian Occupational Performance Measure (COPM) (physician rated)

6.2.2. Efficacy Analysis

6.2.2.1. Movement Disorder-Childhood Rating Scale

The MD-CRS includes 2 parts: part I for general assessment of the patient's functioning and impact of cerebral palsy on the activities of the patient and part II for a specific motor assessment of the severity of the movement disorder. All items are scored on a 5-point ordinal scale (0-4). Zero corresponds to no signs, and 4 corresponds to the most severe findings.

The MD-CRS Part I:

There are 15 items in MD-CRS part I to evaluate the impact of DCP on the activities of the patient and provides a general assessment of the movement disorder of motor function (7 items), oral/verbal function (3 items), self-care (3 items), and attention/alertness (2 items) on a scale of 0 (present) to 4 (absent). Items A1-A7 (Motor function), C1 (Self-dressing) and D1 (Attention/alertness during the observation) are scored by the rater in the clinic and these are video recorded for central reading, all other part I items are scored by the rater based on the parent/caregiver interview. Each item is on a 0 (present) to 4 (absent) scale. The minimum score is 0 and the maximum score is 60.

In case of any missing items, MD-CRS part I total score will be derived by calculating the MD-CRS I index below, and multiplying by the maximum score of 60.

Note that the centrally-read MD-CRS part I total score is obtained by summing the centrally-read items (9 items) and the items that are scored only by the rater in the clinic (6 items). The physician rated MD-CRS part I total score is obtained by summing all 15 items by the rater in the clinic.

MD-CRS Part II:

There are 7 items in MD-CRS part II to evaluate the severity of the movement disorder in a scale of 0 to 4 in 7 body regions. In rating the movement disorder of the body part, 0 refers to absence of a movement disorder and 4 refers to a situation where movement disorder is present during all of the tasks for the region examined and/or involves 3 or more of the other regions, making completion impossible. All items are scored by the rater in the clinic and are centrally read based on video recording. The minimum score is 0 (absent) and the maximum score is 28 (marked/prolonged).

In case of any missing items, MD-CRS part II total score will be derived by calculating the MD-CRS II index below, and multiplying by the maximum score of 28.

The MD-CRS Global Index:

The MD-CRS Global Index is a global measure of the MD-CRS that consolidates the information from parts I and II using the method of weighted means of the 2 normalized indexes obtained from each part. The minimum score is 0 and the maximum score is 1.

The standardized/normalized score for each item of MD-CRS parts I and II with value X is calculated using the formula

$$X_{st} = \frac{X - X_{min}}{X_{max} - X_{min}}$$

where X_{max} is the maximum value for the score, and X_{min} is the minimum value for the score, or 4 and 0 respectively.

The normalized index for the scale, MD-CRS parts I or II, Index I or II, is calculated as the mean value of X_{st}.

The MD-CRS Global Index is the weighted mean of the normalized indexes for MD-CRS parts I and II using the formula:

$$Global\ Index = \frac{n_I \times Index_I + n_{II} \times Index_{II}}{n_I + n_{II}}$$

where n_I and n_{II} are the numbers of items in MD-CRS parts I and II respectively.

The actual values and change from baseline for the MD-CRS Part I, Part II and Global Index scores will be summarized.

6.2.2.2. Caregiver Global Impression of Improvement Scale

CaGI-I is single item questionnaire to assess the caregiver's impression of improvement in dyskinesia symptoms after initiating therapy. It is to be completed before all other investigator-rated scales during visits where CaGI-I is collected. The caregiver has to select the 1 response from the response options that gives the most accurate description of change in dyskinesia symptoms of the patient they care for from the beginning of the study:

1=very much improved (since the initiation of treatment in this study);

2=much improved;

3=minimally improved;

4=no change from day 1 (symptoms remain essentially unchanged);

5=minimally worse;

6=much worse;

7=very much worse (since the initiation of treatment).

The CaGI-I is a single item questionnaire, no impute is used.

The actual value in CaGI-I to each post-baseline visit will be summarized.

6.2.2.3. Clinical Global Impression of Improvement Scale

The Clinical Global Impression of Improvement (CGI-I) is a clinician-reported outcome that uses a 7-point Likert scale that allows the clinician to compare the patient's condition at the visit to the day 1 condition as follows (with anchor points for choosing the most appropriate improvement level):

1=very much improved since the initiation of treatment in this study (nearly all better; good level of functioning; minimal symptoms; represents a very substantial change);

2=much improved (notably better with significant reduction of symptoms; increase in the level of functioning but some symptoms remain);

3=minimally improved (slightly better with little or no clinically meaningful reduction of symptoms; represents very little change in basic clinical status, level of care, or functional capacity);

4=no change from day 1 (symptoms remain essentially unchanged);

5=minimally worse (slightly worse but may not be clinically meaningful; may represent very little change in basic clinical status or functional capacity);

6=much worse (clinically significant increase in symptoms and diminished functioning);

7=very much worse since the initiation of treatment in this study (severe exacerbation of symptoms and loss of functioning).

The CGI-I is a single item questionnaire, no imputation is used.

The actual value in CGI-I to each post-baseline visits will be summarized.

6.2.2.4. Clinical Global Impression of Severity

The Clinical Global Impression of Severity (CGI-S) uses a 7-point Likert scale to assess dyskinesia severity as follows (with anchor points for choosing the most appropriate severity level caused by DCP):

1=normal (not at all ill, symptoms of disorder not present past 7 days);

2=borderline (subtle or suspected pathology);

3=mild (clearly established symptoms with minimal, if any, distress or difficulty in social and/or occupational function);

4=moderate (overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication);

5=marked (intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress);

6=severe (disruptive symptoms, behavior and function are frequently influenced by symptoms, may require assistance from others);

7=extreme (symptoms drastically interferes in many life functions; may be hospitalized).

The CGI-S is a single item questionnaire, no imputation is used.

6.2.2.5. Pediatric Evaluation Disability Inventory-Computer Adapted Test (Activities of Daily Living, Caregiver Completed, Content-Balanced Version

The PEDI-CAT (activities of daily living [ADL], parent/caregiver completed, content balanced version) is a clinical assessment for children and youth. It measures function in 4 domains: (1) Daily Activities; (2) Mobility; (3) Social/Cognitive, and (4) Responsibility. Each domain is self-contained and can be used separately or with other domains. The content balanced version presents a balance of items from each of the Daily Activities domain's content areas (Getting Dressed, Keeping Clean, Home Tasks, and Eating & Mealtime). A total of approximately 30 items are administered (total number of items administered is dependent upon the responses and decision tree path). The PEDI-CAT software utilizes Item Response Theory statistical models to

estimate a child's abilities from a minimal number of the most relevant items or from a set number of items within each domain. All respondents begin with the same item in each domain in the middle of the range of difficulty or responsibility and the response to that item then dictates which item will appear next (a harder or easier item), thus tailoring the items to the child and avoiding irrelevant items. The CAT program then displays the results: normative standard scores, scaled scores and the SE. The scales are available for 21 age groups as intervals of 1 year.

Normative (fit) scores are based on a child's chronological age and intended for use by clinicians so that they may interpret a particular child's functioning relative to others of the same age. This metric is of less relevance for the studied population and therefore will not be assessed.

Scaled scores provide a way to look at a child's current functional skills and progress in these skills over time. Scaled scores are especially helpful in documenting improvements in functional skills for children not expected to exhibit or regain normative levels of functioning. The scaled scores are based on an estimate of the placement of an individual child along the hierarchical scale within each domain. The PEDI-CAT scaled scores are currently on a 20 to 80 scale metric. See PEDI-CAT (Version 1.3.6) Development, Standardization and Administration Manual.

The SE scores indicate the level of the test precision, and are expected to be up to 0.5.

A descriptive summary of the PEDI-CAT scaled score will be provided for all measurements and change from baseline.

6.2.2.6. Unified Huntington's Disease Rating Scale-Total Motor Score

UHDRS-TMS comprises a broad assessment of features associated with Huntington's Disease. The TMS component of UHDRS comprises 31 assessments from the 15 items of the UHDRS. The TMS is calculated as the sum of the 31 motor assessments, each of which range between 0 to 4. The minimum score is 0 (absent) and the maximum score is 124 (worst).

UHDRS-TMC is part of the UHDRS-TMS assessment and assesses the severity of chorea in the face, mouth, trunk, and the 4 extremities. The minimum score is 0 (absent), and the maximum score is 28 (marked/prolonged).

UHDRS-TMD is part of the UHDRS-TMS assessment and assesses the severity of dystonia in the trunk and the 4 extremities. The minimum score is 0 (absent), and the maximum score is 20 (marked/prolonged).

If responses of up to 25% of items are missing in UHDRS-TMS, UHDRS-TMC, or UHDRS-TMD ("scale"), the missing responses will be replaced by the average of the remaining responses within each of the scales. If 8 or more of the items are missing, the missing items will not be replaced and the scale will be set to missing.

The actual values and change from baseline for the UHDRS-TMS, TMC and TMD will be summarized.

6.2.2.7. Canadian Occupational Performance Measure

The COPM has been designed to assess patient outcomes in the areas of self-care, productivity and leisure. Using a semi-structured interview, each patient will identify 5 most important problem areas, and will evaluate performance and satisfaction related to those problem areas.

The COMP performance and satisfaction scale is range from 1 (poor performance or low satisfaction) to 10 (very god performance or high satisfaction).

Total scores are calculated by adding together the performance or satisfaction scores for all problems and dividing by the number of problems. Individual activity problems will be listed.

6.3. Subgroup Analyses

No efficacy subgroup analysis is planned.

7. MULTIPLE COMPARISONS AND MULTIPLICITY

No multiplicity control will be applied to the efficacy analysis or other endpoints.

8. SAFETY ANALYSIS

8.1. General

Safety analyses will be performed on the ITT analysis set, unless otherwise noted. Summaries will be presented by overall patients. Selected safety data might also be presented by age group, as applicable.

For continuous variables, descriptive statistics will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

Summaries of potentially clinically significant abnormal values will include all post-baseline values (including scheduled, unscheduled, and early termination visits).

Safety assessments and time points are provided in Table 3.

8.2. Duration of Exposure to Study Drug

Duration of exposure to study drug (days) for individual patients is the number of days patient received drug (last day of study drug – first day of study drug + 1). Duration of treatment (days) will be summarized using descriptive statistics. Weeks on treatment using the categories ≤4 weeks, >4 to ≤7 weeks, >7 to ≤21 weeks, >21 to ≤27 weeks, >27 to ≤33, >33 to ≤40, >40 to ≤46, >46 to ≤53, and >53 weeks will also be summarized using descriptive statistics.

8.3. Adverse Events

Adverse events will be collected and recorded from the time a patient signs the informed consent to the end of follow-up period. For this study, the follow-up period for recording of adverse events is defined as 2 weeks after the last dose of TEV-50717.

All adverse events will be coded using MedDRA. Each patient will be counted only once in each preferred term or SOC category for the analyses of safety. Unless otherwise specified, adverse events will be summarized by SOC and preferred term, with SOCs and preferred terms within SOCs presented in descending order of patient incidence. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility; see Table 9 of the study protocol - defined as related or with missing relationship), overall and by severity, serious adverse events, and adverse events causing withdrawal from the study; Most common adverse events, defined as occurring in > 4% of the patients in overall, and by preferred term. Summaries will be presented by all patients.

Summaries will include treatment-emergent adverse events which are defined as adverse events occurring at or after the first dose of the IMP. The listings will include all adverse events recorded.

Patient listings of all adverse events, serious adverse events, adverse events leading to study drug discontinuation, adverse events leading to dose interruption and adverse events leading to death will be presented.

8.4. Deaths

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the CSR.

8.5. Clinical Laboratory Tests

Summary statistics for chemistry, hematology and coagulation, and urinalysis laboratory tests are assessed at screening and weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits. Laboratory values and changes from baseline to week 53 will be presented.

A list of laboratory tests is included in Table 10 of the study protocol.

Shifts (below, within, and above the normal range) from baseline to each visit will be summarized using patient counts for all the laboratory tests as applicable. Only patients with both baseline and post-baseline assessments will be summarized in the shift tables.

Only central laboratory assessments will be summarized; local laboratory assessments will be listed. Values below the lower limit of quantification or above the upper limit of quantification will be assessed on a case-by-case basis if present in the data and discussed in the final blinded statistical data review meeting.

8.6. Physical Examinations

Physical examinations will be performed at the time points detailed in Table 4 and Table 5 of the study protocol. Physical examinations will not be summarized. Any finding will be listed.

Weight, height and BMI will be assessed as a part of the vital signs (Section 8.8).

8.7. Neurological Examinations

Neurological examinations will be performed at the time points detailed in Table 4 and Table 5 of the study protocol. Neurological examinations will not be summarized. Any finding will be listed.

8.8. Vital Signs

Vital signs (blood pressure [BP; systolic/diastolic], respiratory rate, body temperature, and pulse) will be measured at the time points detailed in Table 2 and Table 3.

Vital signs values and changes from baseline to each visit will be summarized using descriptive statistics.

Orthostatic systolic and diastolic BP and pulse will be calculated as supine or semi erect/seated measurement minus standing measurement and values and changes from baseline to each visit will be summarized using descriptive statistics.

Orthostatic hypotension (determined by BP measurements only; positive value in case of abnormality) is defined as having either a ≥20 mmHg reduction from supine to standing position in systolic blood pressure (SBP) or ≥10-mmHg reduction from supine to standing position in diastolic blood pressure (DBP) or both. Orthostatic tachycardia is defined as pulse increase ≥20 bpm from supine to standing position.

Summaries of potentially clinically significant abnormal values will include all post-baseline values (including scheduled, unscheduled, and withdrawal visits). The incidence of potentially clinically significant abnormal values will be summarized using descriptive statistics with the criteria specified in Table 8.

Table 8 specifies the criteria for identifying vital signs as potentially clinically significant abnormal values.

Table 8: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign (unit)	Age	Potentially Clinically Significant Low Criterion value	Potentially Clinically Significant High Criterion value
SBP (supine) (mmHg)	6-12	Value ≤70 and≥20 decrease from baseline	Value ≥120 and ≥20 increase from baseline
	13-18	Value ≤ 90 and ≥20 decrease from baseline	Value ≥135 and ≥20 increase from baseline
DBP (supine) (mmHg)	6-12	Value ≤40 and ≥15 decrease from baseline	Value ≥80 and ≥15 increase from baseline
	13-18	Value ≤50 and ≥15 decrease from baseline	Value ≥90 and ≥15 increase from baseline
Pulse rate (supine) (bpm)	6-10	Value ≤60 and ≥15 decrease from baseline	Value ≥135 and ≥15 increase from baseline
	11-18	Value ≤50 and ≥15 decrease from baseline	Value ≥120 and ≥15 increase from baseline
SBP orthostatic criteria (mmHg)	~	≥20 decrease from supine to standing position	NA
DBP orthostatic criteria (mmHg)	~	≥10 decrease from supine to standing position	NA
Pulse rate orthostatic criteria (bpm)	~	NA	≥20 increase from supine to standing position
Temperature (°C)	~	NA	Value ≥38.3°C and ≥0.8°C increase from baseline

The BMI will be computed similarly to description in Section 5.3 at post-baseline visits using weight at visit and last available height measurement.

In addition, normal age and sex-based z-scores and percentiles for BMI will be determined using the WHO growth charts. Age and sex-based BMI categories include: Underweight (< 5 percentile), Normal (≥ 5 - < 85 percentile), Overweight (≥ 85 - < 95 percentile), Obese (≥ 95 percentile).

Descriptive statistics for weight, height and BMI will be provided. Data will be listed.

For COVID-19 updates, vital Signs are optional at week 3 and week 14, mandatory at Week 7, mandatory at Week 27 and at week 40 if not done at the respective previous visit and mandatory at week 53/ET and week 54. Vital Signs can be measured at home, at a local pharmacy or by the home nursing.

Orthostatic blood pressure and pulse are optional.

8.9. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 4 and Table 5 of the study protocol. All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position. A qualified physician at a central diagnostic center will be interpreting the ECG. A central ECG Standard 12-lead ECG will record heart rate (HR), PR interval (Time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram), RR interval (Time between the start of one R wave and the start of the next R wave in the ECG), QT interval, Fridericia's corrected QT interval (QTcF), and QRS duration (Graphical deflections corresponding to ventricular depolarization in a typical electrocardiogram).

All ECG results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

If an abnormal post-baseline QTcF value >500 msec or change from baseline >60 msec is found, the investigator must further evaluate QTcF based on protocol section 7.9.

Shifts (normal and abnormal) from baseline to overall result interpretation and each visit will be summarized using patient counts for the centrally-read interpretation. For overall result interpretation the worst post-baseline finding for the patient (the abnormal finding if there are both normal and abnormal findings) will be used in the summaries. Summary statistics for ECG variables values will be presented. Actual values and changes from baseline to each visit will be summarized using descriptive statistics.

QTcF values will be classified as having QTc prolongation if any of the following conditions are met.

- Confirmed QTcF >450 msec
- Confirmed QTcF>480 msec
- Confirmed QTcF>500 msec
- Increase from baseline QTcF > 60 msec
- Increase from baseline confirmed QTcF > 60 msec

The confirmed QTcF is defined as the average of up to 3 standard ECG values at a visit, or a single summary ECG. If there are more than 3 standard or more than one summary ECG at a visit, then use the last ECGs for the confirmed QTcF.

The number and percentage of patients with QTc prolongation will be summarized overall, and by visit.

The incidence of potentially clinically significant abnormal values for ECG variables will be summarized using descriptive statistics with the criteria presented in Table 9. The summary will be completed by age groups (6 to < 8 years, 8 to < 12 years, 12 to < 16 years, and ≥16 years), and overall.

Table 9: Potentially Clinically Significant Values for ECG Variables by Age

ECG parameter (unit) [a]	Age (years old)	Potentially Clinically Significant Low	Potentially Clinically Significant High
Heart Rate (bpm)	6 to <8	< 65	> 115
	8 to <12	< 55	> 110
	12 to <16	< 50	> 105
	≥16	< 50	> 100
PR interval (msec)	6 to <8	--	> 160
	8 to <12	--	> 175
	12 to <16	--	> 180
	≥16	--	> 200
QRS interval (msec)	6 to <8	--	> 100
	8 to <12	--	> 105
	12 to <16	--	> 110
	≥16	--	> 120

[a] bpm=beats per minute; HR=heart rate; PR interval =Time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram; RR interval =Time between the start of one R wave and the start of the next R wave in the ECG; QRS duration =Graphical deflections corresponding to ventricular depolarization in a typical electrocardiogram

8.10. Concomitant Medications or Therapies

Concomitant therapies and medications, including medications that are taken on an as needed basis and occasional therapies, will be monitored during the study. Details of prohibited medications may be found in Section 8.10 of the study protocol. All concomitant medications will be coded using the WHO Drug.

The incidence of concomitant therapies and medications will be summarized using descriptive statistics by therapeutic class category, preferred base name and preferred term. Patients are counted only once in each therapeutic class, once in each preferred base name and only once in each preferred term category. Concomitant therapies and medications will include all medications taken after the first administration of the IMP up to the end of study as defined in the study protocol.

In order to determine whether a medication is concomitant, partial start dates with missing day and/or month will be imputed with the first day of the month/first month of the year, respectively and partial end dates with missing day and/or month will be imputed with the 28th day of the

month/last month of the year respectively. Imputed dates will be used for calculations only, actual dates will be listed.

Prohibited medications that are associated with QTc prolongation and prohibited antipsychotic drugs are listed in Appendix H, Tables 11 and 12, of the study protocol, respectfully. Any incidence of these prohibited medications will be listed separately.

8.11. Children's Columbia-Suicide Severity Rating Scale

The frequency and severity of suicidal ideation or behavior according to the children's C-SSRS questionnaire will be presented for all patients age ≥12 years by visit. A shift table to examine changes in children's C-SSRS categories from baseline/screening (using the lifetime version of the questions), compared to the worst (highest) category during the treatment period will be presented by all patients and overall.

Patients will be placed into categories for suicidal ideation and suicidal behavior based on their responses to various questions. The suicidal ideation categories will be determined by the following 5 questions.

Table 10: Suicidal Ideation Category

Type	Category
Suicidal Ideation	(0) None – if response is No to Questions 1 and 2 (1) Wish to be Dead – if response to Question 1 is Yes and responses to Questions 2-5 are No. (2) Non-Specific Active Suicidal Thoughts – if response to Question 2 is Yes and response to Questions 3-5 are No. (3) Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act – if response to question 3 is Yes and response to questions 4 and 5 are No. (4) Active Suicidal Ideation with Some Intent to Act, without Specific Plan – if response to Question 4 is Yes and response to Question 5 is No. (5) Active Suicidal Ideation with Specific Plan and Intent – if response to Question 5 is Yes.

For suicidal behavior, the following categories will be used. The categories will be determined based on the response to the questions.

Table 11: Suicidal Behavior Category

Type	Category
Suicidal Behavior	(6) Preparatory Acts or Behavior – if response to Preparatory Acts and Behavior is Yes and responses to Actual Attempt, Interrupted Attempt, Aborted Attempt, and Completed Suicide are No (7) Aborted Attempt – if response to Aborted Attempt is Yes and responses to Actual Attempt, Interrupted Attempt, and Completed Suicide are No. (8) Interrupted Attempt – if response to Interrupted Attempt is Yes and response to Actual Attempt, and Completed Suicide are No. (9) Actual Attempt – if response to Actual Attempt is Yes and Completed Suicide is No. (10) Completed Suicide - if response to Completed Suicide is Yes (0) None – if responses to all the above questions are No.

Suicidal ideation or behavior will be derived as the highest suicidal ideation or behavior score at the visit. Score of 0 represent "No Suicidal Ideation/Behavior".

The frequency and percentage of suicidal ideation, suicidal behavior, suicidal ideation or behavior, and self-injurious behavior without suicidal intent will be summarized by treatment and overall, and visit.

8.12. Child Behavior Checklist for Ages 6-18 (CBCL)

The CBCL assesses behavioral and emotional status in children ages 6 through 18 years of age as reported by the parent/caregiver (Achenbach and Ruffle 2000; Achenbach 2005). The full CBCL has 2 parts, a Competence Scale (Parts I to VII) and a Syndrome Scale (behavioral items).

8.12.1. Competence Scale

The Competence Scale (Parts I to VII) assesses various activities, interpersonal relationships, and academic performance. Competence assessment will be performed at screening or day 1 visit and at the 53/ET visit.

The competence scale is divided into 3 subscales – see Table 12.

Table 12: CBCL Competence Scale

Activities	Social	School
I.A. number of sports	III.A. number of organizations	VII.1. Mean performance
I.B. Mean part/skills	III.B. Mean Participation	VII.2. Special class
II.A. number of activities	V.1 number of friends	VII.3. Repeated grade
II.B. Mean part/skills	V.2 Frequency of contact	VII.4. School problems
IV.A. number of jobs	VI.A. Behavior with others	
IV.B. Mean job quality	VI.B. Behavior alone	

Total score and change from baseline for each subscale separately and a total score and change from baseline for all items will be summarized for each time point using descriptive statistics for continuous variables. Total scores are rounded to nearest 0.5.

Scores per item are calculated as follows in Table 13:

Table 13: CBCL Competence Scale Scoring

Subscale	Item	Scoring
Activities	I.A. number of sports	count the number of sports.
	I.B. Mean part/skills	mean of up to 6 rates, 2 for each sport activity. Where 'below average' or 'Less than average'=0, 'Average'=1, 'above average' or 'More than average'=2.
	II.A. number of activities	count the number of activities.
	II.B. Mean part/skills	mean of up to 6 rates, 2 for each activity. Where 'below average' or 'Less than average'=0, 'Average'=1, 'above average' or 'More than average'=2.
	IV.A. number of jobs	count the number of jobs.
	IV.B. Mean job quality	mean of up to 3 rates, 1 for each job. Where: 'below average'=0, 'Average'=1, 'above average'=2.
Social	III.A. number of organizations	count the number of organizations.
	III.B. Mean Participation	mean of up to 3 rates, 1 for each organization. Where: 'Less active'=0, 'Average'=1, 'More active'=2.
	V.1 number of friends	None'=0, '1'=1, '2 or 3' =2, '4 or more'=3.
	V.2 Frequency of contact	'Less than 1'=0, '1 or 2'=1, '3 or more'=2.
	VI.A. Behavior with others	mean of items a-c. Where: 'Worse'=0, 'Average'=1, 'Better'=2.
	VI.B. Behavior alone	rate for item d. Where: 'Worse'=0, 'Average'=1, 'Better'=2.
School	VII.1. Mean performance	Mean of up to 7 performance items. Where 'failing'=0, 'below average'=1, 'average'=2,'above average'=3.
	VII.2. Special class	'Yes='0', 'No='1'.
	VII.3. Repeated grade	'Yes='0', 'No='1'.
	VII.4. School problems	'Yes='0', 'No='1'.

Values of 'Do not know', 'Not applicable', or 'Has no brothers or sisters' will be ignored for mean calculations and logically skipped items will be imputed as 0 or none.

A subscale score is calculated as the sum of the item scores and the total score is calculated as the sum of the subscale scores. If one or more subscale scores are missing, the total score will not be calculated.

If 1 item from activities and social subscales has a missing value, the mean of the other items of that subscale is substituted for that item. If more than 1 item is missing from either of these scales or any item is missing from the school scale, the respective scale is not to be scored.

Results will be listed.

8.12.2. Syndrome Scale

The Syndrome Scale comprises 113 questions related to problem behaviors. Syndrome assessment will be performed at day 1, and at weeks 3, 7, 14, 27, 40, and 54/follow-up visits.

For each item, the parent/caregiver will circle '0' if the item is not true of their child, '1' if the item is somewhat or sometimes true, and '2' if the item is very true or often true.

The Syndrome scale is divided into 8 subscales – see Table 14.

Table 14: CBCL Syndrome Scale

Anxious / Depressed		**Withdrawn / Depressed**	**Somatic Complaints**	**Social Problems**	**Thought Problems**	
14.Cries 30.FearsSchool 32.Perfect 35.Worthless 50.Fearful 71.SelfConsc 112.Worries	29.Fears 31.FearDoBad 33.Unloved 45.Nervous 52.Guilty 91.ThinksSuicide	5.EnjoysLittle 42.RatherBeAlone 65.Won'tTalk 69.Secretive 75.Shy 102.LacksEnergy 103.Sad 111.Withdrawn	47.Nightmares 49.Constipated 51.Dizzy 54.Tired 56a-g.Physical Problems without known medical cause[a]	11.Dependent 12.Lonely 25.NotGetAlong 27.Jealous 34.OutToGet 36.Accidents 38.Teased 48.NotLiked 62.Clumsy 64.PreferYoung 79.SpeechProb	9.MindOff 40.HearsThings 58.PicksSkin 60.SexPartsM 70.SeesThings 83.StoresUp 85.StrangeIdeas 100.SleepProb	18.HarmsSelf 46.Twitches 59.SexPartsP 66.RepeatsActs 76.SleepsLess 84.StrangeBehav 92.SleepWalk
Rule-Breaking Behavior		**Attention Problems**	**Aggressive Behavior**		**Other Problems**	
2.Alcohol 28.BreaksRules 43.LiesCheats 67.RunAway 73.SexProbs 82.StealsOther 96.ThinksSex 101.Truant 106.Vandalism	26.LacksGuilt 39.BadFriends 63.PreferOlder 72.SetsFires 81.StealsHome 90.Swears 99.Tobacco 105.UsesDrugs	1.ActsYoung 4.FailsToFinish 8.Concentrate 10.SitStill 13.Confused 17.Daydreams 41.Impulsive 61.PoorSchool 78.Inattentive 80.Stares	3.Argues 19.DemAtten 21.DestroyOther 23.DisobeySchl 57.Attacks 86.Stubborn 88.Sulks 94.Teases 97.Threaten	16.Mean 20.DestroyOwn 22.DisobeyHome 37.Fights 68.Screams 87.MoodChang 89.Suspicious 95.Temper 104.Loud	6.BMOut 15.CruelAnimal 44.BiteNail 55.Overweight 74.ShowsOff 93.TalkMuch 107.WetsSelf 109.Whining 113.OtherProb[b]	7.Brags 24.NoEatWell 53.Overeat 56h.OtherPhys 77.SleepsMore 98.ThumbSuck 108.WetsBed 110.WishOppSex

[a] Item 56 stands for "Physical Problems without known medical cause: other" and may not be filled in by the responder.
[b] Similarly, item 113 that stands for "Any problems that were not listed above" may be missing, for the same reason.

Total score for each subscale separately, total score for all items, change from baseline for the total score for each subscale separately and change from baseline for total score for all items will be summarized for each time point using descriptive statistics for continuous variables.

Total score is calculated as the sum of items scores.

If more than 20 items have missing values, excluding items 56h and 113, which may be left blank by structure (see Table 14 for details), then no scores will be provided. For calculating subscale scores, if one or more items, excluding items 56h and 113, are missing in a subscale, the subscale score will not be calculated.

Data will be listed.

8.13. Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire composed of 8 questions that provide a measure of a patient's general level of daytime sleepiness (Johns 1991).

The ESS is administrated at screening and/or day 1 visit, and administered at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits.

The ESS is composed of 8 items. The responders are asked to rate their chances of falling asleep while engaged at 8 different activities, on a 4-point scale (0-3). Therefore, the total score can range from 0 to 24.

If at least 1 item has a missing value, then the entire questionnaire is not valid.

Total score of the 8 items and total scores change from baseline will be summarized by time point, using descriptive statistics. In the case of both caregiver and self-administered versions of the ESS are presented at the same visit, caregiver version will be used for patients who are 6 to 12 years old and self-administered version will be used for patients 13 years of age and older.

Total score is calculated as the sum of item scores.

Data will be listed.

8.14. Extrapyramidal Symptom Rating Scale

The Extrapyramidal Symptom Rating Scale (ESRS) consists of 2 subscales, ESRS I and ESRS II.

ESRS I and II are administrated at the baseline/day 1 visit and administered at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits.

8.14.1. ESRS I

The first subscale (ESRS I) is a 7 item subjective questionnaire to evaluate parkinsonism, akathisia, dystonia and dyskinesia. The ESRS I is scored on for point scale (0=absent, 1=Mild, 2=Moderate, Severe=3) for each item.

Total score will be the sum of the 7 items. Missing item will be replaced by the average of the remaining responses within each item.

Total score and total scores change from baseline will be summarized by time point, using descriptive statistics.

Data will be listed.

8.14.2. ESRS II

The second subscale (ESRS II) is a 17-item questionnaire to evaluate parkinsonism and akathisia.

ESRS II consists of the following parts:

1. Tremor: scored on a 7-point item scale for 8 parts of the body. For each part of the body, frequency and amplitude are selected, assigning each one of the 8 items a score from 0=none to 6=severe. Therefore, the total score for tremor can ranged from 0 to 48.
2. Bradykinesia: scored on a 7-point item scale (0-6).
3. Gait and Posture: scored on a 7-point item scale (0-6).
4. Postural stability: scored on a 7-point item scale (0-6).
5. Rigidity: scored on a 7-point item scale (0-6) for 4 parts of the body. Therefore, the total score for rigidity can ranged from 0 to 24.
6. Expressive automatic movements: scored on a 7-point item scale (0-6).
7. Akathisia: scored on a 7-point item scale (0-6).

The total score of the 17 items can ranged from 0 to 102.

Total score will be the sum of the 17 items. Missing item will be replaced by the average of the remaining responses within each item.

Total score and total scores change from baseline will be summarized by time point, using descriptive statistics for continuous variables.

Data will be listed.

9. TOLERABILITY VARIABLES AND ANALYSIS

If more than 15% of the patients withdraw from the study before the end of the treatment period, the number of days until study discontinuation will be analyzed using Kaplan-Meier methodology with the ITT analysis set.

10. STATISTICAL SOFTWARE

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

11. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

Not applicable.

12. REFERENCES

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