Clinical Study Protocol

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

Protocol with Amendment 04 Approval Date: 01 June 2022

Clinical Study Protocol with Amendment 04

Study Number 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 in Children and Adolescents (Open RECLAIM-DCP)

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

IND Number: 139700; NDA Number: NA; EudraCT Number: 2019-001807-19

EMA Decision Number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

Original Protocol Approval Date: 07 March 2019
Protocol Amendment 04 Approval Date: 01 June 2022

Sponsor

Teva Branded Pharmaceutical
Products R&D, Inc.
145 Brandywine Parkway
West Chester, Pennsylvania 19380
United States of America

Information regarding clinical laboratories and other departments and institutions is found in Appendix A

COVID-19 pandemic-related operational updates are provided in Appendix M

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

Confidentiality Statement

AMENDMENT HISTORY

The protocol for Study TV50717-CNS-30081 (original protocol dated 07 March 2019) has been amended and reissued as follows:

Amendment 04	01 June 2022 42 patients enrolled to date
Administrative Letter 06	11 June 2021
Administrative Letter 05	23 February 2021
Administrative Letter 04	14 November 2020
Administrative Letter 03	14 July 2020
Amendment 03	23 June 2020 8 patients enrolled to date
Amendment 02	19 March 2020 3 patients enrolled to date
Amendment 01	02 October 2019 0 patients randomized/enrolled to date
Letter of Clarification 02	02 July 2019
Letter of Clarification 01	07 June 2019

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.

INVESTIGATOR AGREEMENT

Original Protocol Dated 07 March 2019
Amendment 04 Dated: 01 June 2022

IND Number: 139700; NDA Number: NA; EudraCT Number: 2019-001807-19

EMA Decision Number of Pediatric Investigation Plan: Not Applicable

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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)

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with amendment 04 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, investigational medicinal products (IMP) shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations.

Principal Investigator	**Signature**	**Date**

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]		

Executed signature pages are maintained separately within the Trial Master File

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 07 March 2019
Amendment 04 Dated: 01 June 2022

IND Number: 139700; NDA Number: NA; EudraCT Number: 2019-001807-19

EMA Decision Number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

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)

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I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on patient information, IMPs shipment and return forms, and other information collected during the study, in accordance with my responsibilities under the function of the coordinating investigator and in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations. In addition I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator: [redacted]

Title: [redacted]

Address of Investigational Center: Vanderbilt University Medical Center
Department of Neurology
1161 21st Avenue South
A-0118 MCN
Nashville, TN 37232-2551

Tel: [redacted]

Coordinating Investigator [redacted]	**Signature** *Signed page is retained in the sponsor's official repository.*	**Date**

Executed signature pages are maintained within the Investigator Site File and Trial Master File.

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 07 March 2019
Amendment 04 Dated: 01 June 2022

IND Number: 139700; NDA Number: NA; EudraCT Number: 2019-001807-19

EMA Decision Number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

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)

I have read the protocol with amendment 04 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national and local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on patient information, IMPs shipment and return forms, and other information collected during the study, in accordance with my responsibilities under the function of the coordinating investigator and in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations. In addition I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator: [redacted]

Title: [redacted] at Children's of Alabama Hospital

Address of Investigational Center: 1600 7th Ave. S.
CHB Suite 314
Birmingham, AL 35233

Tel: [redacted]

Coordinating Investigator [redacted]	**Signature** *Signed page is retained in the sponsor's official repository.*	**Date**

Executed signature pages are maintained within the Investigator Site File and Trial Master File.

CLINICAL STUDY PROTOCOL SYNOPSIS

Study TV50717-CNS-30081

Title of Study: 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)

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc., 145 Brandywine Parkway, West Chester, Pennsylvania 19380, United States of America

Investigational New Drug (IND) Number: 139700

New Drug Application (NDA) Number: Not applicable

EudraCT Number: 2019-001807-19

EMA Decision Number of Pediatric Investigation Plan: Does not apply

Name of Active Ingredient: Deutetrabenazine

Name of Test Investigational Medicinal Product (IMP): TEV-50717 (deutetrabenazine, previously SD-809)

Type of Study: Safety and Efficacy (Phase 3)

Indication: Dyskinesia in cerebral palsy (DCP)

Is this study conducted to investigate the New Use of an approved, marketed product? Yes

Number of Investigational Centers Planned: The study is planned to be conducted in approximately 35 investigational centers.

Countries Planned: Global (per Study TV50717-CNS-30080)

Planned Study Period: Q1 2020 to Q4 2023 with a duration of approximately 55 weeks

Number of Patients Planned (total): Approximately 45 patients

Study Population: Male and female children and adolescents diagnosed with DCP who have previously completed participation in parent Study TV50717-CNS-30080.

Primary and Secondary Objectives and Endpoints: The primary and secondary study objectives and endpoints are presented 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 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
The **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 (activities of daily living, caregiver completed, content-balanced version) • UHDRS-TMC (centrally read) • UHDRS-TMD (centrally read) • UHDRS-TMS (physician rated) • 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; 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.

General Study Design: This is a 55-week, open-label, single-arm study in which patients who have successfully completed the parent 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. Any patient who cannot enroll within this timeframe, for any justified reason, must be discussed and pre-approved by the medical monitor prior to enrolling the patient. 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. 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.

For the purposes of this protocol, a caregiver is defined as an adult, who is familiar with the patient and responsible for daily care, enabling that person to effectively complete the protocol requirements. The caregiver accompanies the patient to the visits and provides input to the relevant scales as required by the protocol.

For patients who are minors, the caregiver is typically a parent or legally acceptable representative. In some countries, an adult (such as grandparent or nurse) may be appointed by the parent or legally acceptable representative (as per local regulations and laws) and would take over this responsibility as caregiver. The parent or legally acceptable representative only has to sign the parent/legally acceptable representative informed consent form (ICF) and not the caregiver ICF.

For adult patients, a caregiver must be appointed by the patient. The caregiver can be the parent or other adult as appropriate and according to local laws and regulations.

For patients who are minors, certain responsibilities in the protocol can only be completed by the parent/legally acceptable representative; ie, informed consent, withdrawal of consent, requests for discontinuation of IMP, or withdrawal from the study for any reason. To further clarify, the caregiver is not allowed to make decisions on the child's health, or where "parent/legally acceptable representative" is specifically indicated in the protocol.

Site-administered scales include the Movement Disorder-Childhood Rating Scale (MD-CRS) parts I and II (physician rated, with video recording), Caregiver Global Impression of Improvement (CaGI-I), Clinical Global Impression of Improvement (CGI-I), Clinical Global Impression of Severity (CGI-S), Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI-CAT), Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS), Unified Huntington's Disease Rating Scale-Total Maximal Chorea (UHDRS-TMC),

Unified Huntington's Disease Rating Scale-Total Maximal Dystonia (UHDRS-TMD), Canadian Occupational Performance Measure (COPM), children's Columbia-Suicide Severity Rating Scale (C-SSRS), Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II, Child Behavior Checklist (CBCL) for ages 6 to 18 years, and Epworth Sleepiness Scale (for children and adolescents) (ESS) questionnaire. Children 13 years of age and under must be interviewed in conjunction with the caregiver. For children over 13 years of age, questions should be directed to the child; however, caregiver involvement is strongly encouraged to add relevant information.

In the study period descriptions below, "week X" refers to the end of that week, which coincides with the study visit, unless stated otherwise. Some dose changes will occur at the start of a week rather than at the end of a week and will be indicated as such.

Patients can either enroll in the study at the week 16 visit of Study TV50717-CNS-30080 or up to 4 weeks 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 (Figure 2).

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 the most current, **do not** need to be repeated, except for orthostatic pulse rate and blood pressure, electrocardiogram (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.

In addition, the following applies for day 1 baseline assessments for this study:

- clinically significant laboratory abnormalities identified at week 15 in Study TV50717-CNS-30080 are to be repeated at week 16 of the parent study for eligibility in Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. Any abnormalities which are listed in the inclusion/exclusion criteria must be discussed with the medical monitor prior to patient enrollment into the study.
- urine drug screen is performed at week 16 in study TV50717-CNS-30080 and will serve as day 1 baseline values in this study.
- 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.
- weight is performed at week 16 in Study TV50717-CNS-30080 and height is performed at week 15 in study TV50717-CNS-30080; these assessments will serve as day 1 baseline values in this study.

- vital signs (respiratory rate and body temperature) are performed at week 16 in 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, these assessments will serve as day 1 baseline values in this study. Otherwise, these assessments will be performed at day 1.
- physical and neurological examinations are performed at week 15 (and week 16, if applicable) in Study TV50717-CNS-30080. The findings from the last assessment taken will serve as day 1 baseline values in this study.
- ECG is to be performed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study.
- medical and psychiatric history are to be assessed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study.
- COPM (an assessment included only in Study TV50717-CNS-30081) will also be performed at day 1.

At the investigator's discretion, abnormal findings can be discussed with the medical monitor.

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 4, 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 4. 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.

For patients who enroll in the study between 2 and ≤4 weeks after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.

Titration period (7 weeks): Because the patients from parent Study TV50717-CNS-30080 have discontinued TEV-50717 treatment for at least 1 week at completion of the parent study or received placebo in the parent study, 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 (Table 2). 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 TEV-50717 tablets cannot be crushed or split but should be swallowed whole; the TEV-50717 tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. The titration scheme and maximum dose will be determined by body weight at day 1 and cytochrome P450 2D6 (CYP2D6) impairment status, as shown in Table 2 and Table 3, respectively. 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, as shown in Table 3.

Patients and their caregiver will interact weekly with the clinical research staff, either by telephone contact (with non-recording live video) or in-clinic visits from week 1 through week 7 of the titration period, in order to evaluate safety and establish a dose of TEV-50717 that optimally reduces dyskinesia (as indicated by a reduction in the CGI-I) and is well tolerated (optimal dose). The telephone contacts to the patient will be supported by live video stream, without recording, to provide visual confirmation to the investigator of the verbal information provided by the patient or caregiver. Safety evaluations during the titration period include assessment of vital signs, monitoring for adverse events and concomitant medications, 12-lead ECGs, identifying patients at risk for suicide, assessment of drug-induced parkinsonism according to the ESRS (subscales I and II), assessment of change in behavior according to the CBCL questionnaire, and assessment of sedation according to the 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.

The dose of TEV-50717 should be increased to reach a clinically meaningful reduction in dyskinesia, as indicated by a reduction in the CGI-I (see Table 2). The dose of TEV-50717 should not be increased further if either of the following occurs:

- the patient experiences a “clinically significant” adverse event (defined as an adverse event that is related to TEV-50717 and is either moderate or severe in intensity or meets the criteria for a serious adverse event), OR
- the maximum allowable dose is reached based on the patient’s weight and CYP2D6 impairment status at day 1. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor.

Dose adjustments can be made up to and including the week 7 in-clinic visit. If an optimal dose is reached before the week 7 in-clinic visit, the dose of TEV-50717 should not be increased further, but the patient should continue on that dose for the remainder of the titration period. If a patient experiences a “clinically significant” adverse event attributable to TEV-50717, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible. If the determination that a patient requires a dose reduction or suspension is made during a telephone contact, an unscheduled clinic visit should be conducted as soon as practicable thereafter.

Dose adjustments should be made based on all available information, including the patient and caregiver reports of adverse events and dyskinesia reduction, the clinical assessment of safety and efficacy by the investigator, and the information from rating scales.

Table 2: Maximum Daily Dose of TEV-50717 by Week and Weight Category on Day 1 for Titration at Study Initiation

Study time period	Daily dose[a], [b]			
	12 kg to <17 kg (26 lbs to <37 lbs)	17 kg to <30 kg (37 lbs to <66 lbs)	30 kg to <40 kg (66 lbs to <88 lbs)	≥40 kg (≥88 lbs)
Day 2 (first dose in morning)	6 mg	6 mg	6 mg	6 mg
Week 1	6 mg	6 mg	6 mg	12 mg[c]
Week 2	6 mg	12 mg	12 mg	18 mg
Week 3	12 mg[d]	18 mg	18 mg	24 mg
Week 4	12 mg[d]	18 mg[d]	24 mg[d]	30 mg
Week 5	18 mg[d]	24 mg[d]	30 mg[d]	36 mg[d]
Week 6	18 mg[d]	24 mg[d]	36 mg[d]	42 mg[d]
Week 7	24 mg[d]	30 mg[d]	42 mg[d]	48 mg[d]

[a] All IMP adjustments are made only after a remote or in-clinic visit; if the dose is escalated, the dose escalation will occur with the next morning's dose. Dose adjustments should ONLY take place after a telephone or in-clinic visit.
[b] Dose increases may not occur more frequently than every 5 days, except for patients ≥40 kg/88 lbs. For patients ≥40 kg/88 lbs, the first dose increase should be performed in an interval less than 5 days, only once, on day 3. Refer to Table 5 for the exact visit windows at each weekly titration visit.
[c] Patients in this weight category will receive the 6 mg once-daily dose in the morning on day 2, followed by twice daily administration of 6 mg starting on day 3.
[d] For those taking strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, and bupropion, the maximum daily dose for patients ≥40 kg is 36 mg/day, that for 30 to <40 kg is 24 mg/day, that for 17 to <30 kg is 18 mg/day, and that for 12 to <17 kg is 12 mg/day (see Table 3).
CYP2D6=cytochrome P450 2D6.

Table 3: Maximum Daily Dose of TEV-50717 by CYP2D6 Impairment Status

Weight category	Maximum daily dose in the absence of CYP2D6 impairment	Maximum daily dose in the presence of CYP2D6 impairment
12 kg to <17 kg (26 lbs to <37 lbs)	24 mg	12 mg
17 kg to <30 kg (37 lbs to <66 lbs)	30 mg	18 mg
30 kg to <40 kg (66 lbs to <88 lbs)	42 mg	24 mg
≥40 kg (≥88 lbs)	48 mg	36 mg

CYP2D6=cytochrome P450 2D6.
Note: Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor. Strong CYP2D6 inhibitors include paroxetine, fluoxetine, and bupropion.

Maintenance period (46 weeks): At the end of the titration period (week 7 visit), 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. As during titration, dose adjustments should be made based on all available information. Dose reductions of TEV-50717 or suspensions of patients for adverse events or tolerability findings are allowed.

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, including vital signs and weight, physical and neurological examination, height measurement, 12-lead ECG, safety laboratory testing, urine drug screen, and beta-human chorionic gonadotropin (β-HCG) test, when applicable, as well as the MD-CRS parts I and II, CaGI-I, CGI-I, CGI-S, PEDI-CAT, UHDRS-TMS, UHDRS-TMC, UHDRS-TMD, COPM, children's C-SSRS assessments, ESRS (subscales I and II), CBCL, and ESS.

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).

Brief Summary of Study Design for the Trial Registry(s):

Study TV50717-CNS-30081 is a 55-week 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 period where no treatment is administered and the final evaluation at week 16. Patients may roll over from Study TV50717-CNS-30080 on the same day as the week 16 visit or up to 4 weeks from the week 15 visit of the TV50717-CNS 30080 study. Any

patient who cannot enroll within this timeframe, for any justified reason, must be discussed and pre-approved by the medical monitor prior to enrolling the patient. 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 is an open-label study, and all patients who are enrolled will receive TEV-50717; there is no placebo treatment group. The purpose of the study is to determine whether long-term treatment with TEV-50717 is safe, tolerable, and effective in the treatment of dyskinetic involuntary movements associated with CP.

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, 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. 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.

Approximately 45 patients who have completed parent Study TV50717-CNS-30080 are planned for enrollment into this study.

Patients can either enroll in the study at the week 16 visit of Study TV50717-CNS-30080 or up to 4 weeks following the week 15 visit. 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 (Figure 2).

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, electrocardiogram (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.

In addition, the following applies for day 1 baseline assessments for this study:

- clinically significant laboratory abnormalities identified at week 15 in Study TV50717-CNS-30080 are to be repeated at week 16 of the parent study for eligibility in Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. Any abnormalities which are listed in the inclusion/exclusion criteria must be discussed with the medical monitor prior to patient enrollment into the study.
- Urine drug screen is performed at week 16 in study TV50717-CNS-30080 and will serve as day 1 baseline values in this study.

- 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.
- weight is performed at week 16 in Study TV50717-CNS-30080 and height is performed at week 15 in study TV50717-CNS-30080; these assessments will serve as day 1 baseline values in this study.
- vital signs (respiratory rate and body temperature) are performed at week 16 in 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, these assessments will serve as day 1 baseline values in this study. Otherwise, these assessments will be performed at day 1.
- physical and neurological examinations are performed at week 15 (and week 16, if applicable) in Study TV50717-CNS-30080. The findings from the last assessment taken will serve as day 1 baseline values in this study.
- ECG is to be performed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study.
- medical and psychiatric history are to be assessed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study.
- COPM (an assessment included only in Study TV50717-CNS-30081) will also be performed at day 1.

At the investigator's discretion, abnormal findings can be discussed with the medical monitor.

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 4, 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 4. 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.

For patients who enroll in the study between 2 and ≤4 weeks after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.

Because the patients from parent Study TV50717-CNS-30080 have discontinued TEV-50717 treatment for at least 1 week at completion of the parent study or received placebo in the parent study, all patients will undergo TEV-50717 dose titration (7 weeks) in this study in order to maintain the blind of the parent Study TV50717-CNS-30080. Patients will receive 6 mg of TEV-50717 (Table 6). 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 TEV-50717 tablets cannot be crushed or split, but should be swallowed whole; the TEV-50717 tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. The titration scheme and maximum dose will be determined by body weight at day 1 and 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 this study. Patients and their caregiver will interact weekly with the clinical research staff, either by telephone contact or in-clinic visits from week 1 through week 7 of the titration period, in order to evaluate safety and establish a dose of TEV-50717 that optimally reduces dyskinesia (as indicated by a reduction in the CGI-I) and is well tolerated (optimal dose). The telephone contacts to the patient will be supported by live video stream, without recording, to provide visual confirmation to the investigator of the verbal information provided by the patient or caregiver.

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

The dose of TEV-50717 should be increased to reach a clinically meaningful reduction in dyskinesia, as indicated by a reduction in the CGI-I (see Table 2). The dose of TEV-50717 should not be increased further if either of the following occurs:

- the patient experiences a “clinically significant” adverse event (defined as an adverse event that is related to TEV-50717 and is either moderate or severe in intensity or meets the criteria for a serious adverse event), OR
- the maximum allowable dose is reached based on the patient’s weight and CYP2D6 impairment status at day 1. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor.

Dose adjustments can be made up to and including the week 7 in-clinic visit. If an optimal dose is reached before the week 7 in-clinic visit, the dose of TEV-50717 should not be increased further, but the patient should continue on that dose for the remainder of the titration period. If a patient experiences a “clinically significant” adverse event attributable to TEV-50717, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible. If the determination that a patient requires a dose reduction or suspension is made during a telephone contact, an unscheduled clinic visit should be conducted as soon as practicable thereafter.

Dose adjustments should be made based on all available information, including the patient and caregiver reports of adverse events and dyskinesia reduction, the clinical assessment of safety and efficacy by the investigator, and the information from rating scales.

During the maintenance period (week 8 to week 53), dose adjustments of TEV-50717 (upward or downward) may be made, 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. 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 will be scheduled for weeks 21, 33, and 46 in order to assess adverse events and dyskinesia.

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 for safety evaluation 1 week after the end of the washout period (ie, the period where no treatment is administered), which will be 2 weeks after their last dose of TEV-50717 (week 55).

Method of Randomization and Blinding: Not applicable. This is an open-label, single-arm study with no blinding.

Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate:

Test IMP is defined as TEV-50717 (deutetrabenazine, previously SD-809) in this study.

Test IMP will be administered as oral tablets at a starting dose of 6 mg once daily. Titration schemes based on body weight at day 1 are shown in Table 2. The maximum daily dose is determined by body weight at day 1 and CYP2D6 impairment status (Table 3). Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor. If a patient experiences a “clinically significant” adverse event that is attributed to TEV-50717, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible. At the end of the titration period, the patient’s initial dose will be established for the maintenance period. 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. As during titration, dose adjustments should be made based on all available information. The dose of TEV-50717 may be reduced or suspended if a patient experiences an adverse event or tolerability finding during the maintenance period and the investigator believes a dose reduction or suspension is warranted.

TEV-50717 oral tablets (test IMP) are 6, 9, and 12 mg, or other commercially available, dose strengths. Each dose strength will have a marking corresponding to the dose strength on the label. TEV-50717 will be supplied as 60-count tablets per bottle. Each dose strength will be a colored tablet with a marking of “SD” and the corresponding strength.

All IMP adjustments are made only after a remote or in-clinic visit; if the dose is escalated, the dose escalation will occur with the next morning’s dose.

TEV-50717 will be administered as follows:

- TEV-50717 cannot be crushed or split but should be swallowed whole; the TEV-50717 tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. Patients may be offered the optional use of a Medi+Straw®, which is a commercially available straw that can assist patients to overcome their swallowing difficulties.

- Dosing and titration will be based on body weight at the day 1 visit and CYP2D6 impairment status, as shown in Table 2 and Table 3, respectively.
- The starting dose is 6 mg in all patients. 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. If a patient misses a dose, and it is within 6 hours of the next dose, the missed dose should be skipped. If a patient is on the 6 mg once daily dose (12 kg to <17 kg; 26 lbs to <37 lbs) and experiences somnolence while taking the 6-mg dose in the morning, he/she may switch to taking it as an evening dose for the rest of the days up to day 14.
- 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.
- 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.
- 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.
- At an in-clinic visit, a dose reduction, if required, should be made to the previously tolerated dose level. **If more than 1 dose reduction is required for an adverse event, the medical monitor should be notified.**
- During the titration period, the dose of TEV-50717 should be adjusted according to Table 2 to identify a dose level that optimally reduces dyskinesia (as determined by the investigator, as indicated by a reduction in the CGI-I) and is well tolerated. Dose adjustments should ONLY take place after a telephone or in-clinic visit.

Test IMP: TEV-50717 (deutetrabenazine, previously SD-809)

Placebo IMP: Not applicable

Duration of Patient Participation and Maximal Exposure to IMP: All participating patients are expected to participate in this study for its entire duration, which is 55 weeks. Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of TEV-50717). Any patient that reaches the age of legal competence to give informed consent during the course of Study TV50717-CNS-30081 will need to be re-consented as an adult. When a patient is a minor advancing to the next age range (new assent available and patient is still considered a minor by local law), the patient may need to sign on new assent appropriate for that age in order to continue participation in the study (in accordance with local laws and regulations).

Study Duration: Approximately 55 weeks

End of Study: The end of the study TV50717-CNS-30081 is defined as the date of the week 55 follow-up telephone contact of the last participant.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: There are no plans to provide further treatment to patients upon completion of the study. An extension to the study may be considered on an annual basis.

Inclusion Criteria: Patients who meet the criteria below are eligible to be included in the study.

a. Patient has completed week 16 of Study TV50717-CNS-30080.

b. Patient weighs at least 12 kg (26 lbs) on day 1 of this study.

c. Patient is able to swallow TEV-50717 whole.

d. Patient and caregiver are willing to adhere to TEV-50717 regimen and comply with all study procedures.

e. Patient is in good general health, as indicated by medical and psychiatric history and physical and neurological examination.

f. In the investigator's opinion, the patient and/or caregiver has the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed.

g. For a patient who is a minor, the parent(s)/legally acceptable representative(s) provides written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide written informed consent (in accordance with local regulations), and the legally acceptable representative will sign, if needed.

   In this study, eligible patients with dyskinetic cerebral palsy may have some degree of mental, motor, and/or communication (eg, speech, writing, etc.) limitations or disabilities. The patient may not be able to read the assent/consent form. Some patients may only be able to provide a limited assent/consent (for instance, by verbalizations or gestures). The investigator will determine the suitability of enrolling such patients in this study and will follow the local regulation to obtain the relevant consent/assent.

h. A caregiver provides written informed consent after being assigned the role by an adult patient or if this role is delegated by the parent/legally acceptable representative of a patient who is a minor.

i. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β-HCG test on day 1 or are sterile.

j. Females who are postmenarchal or ≥12 years of age whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting day 1) and for 30 days after last dose of TEV-50717.

Exclusion Criteria: Patients will not be randomized/enrolled in this study if they meet any of the following criteria:

a. Patient has clinically significant depression at screening or day 1 of this study.

- Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening or day 1 (whichever comes first) and anticipated to remain stable (dose and frequency) within the study duration.

b. Patient has a history of suicidal intent or related behaviors based on medical or psychiatric history or the C-SSRS at screening visit, if performed, or at the day 1 visit, as applicable according to the patient's age:
   - intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence, at the time of suicidal thought
   - suicidal preparatory acts or behavior

c. Patient has a history of a previous actual, interrupted, or aborted suicide attempt based on medical or psychiatric history or the C-SSRS at screening visit, if performed, or at the day 1 visit, as applicable according to the patient's age.

d. Patient has a first-degree relative who has completed suicide.

e. Patient has received any of the following concomitant medications within the specified exclusionary windows from screening or day 1 (whichever comes first) of this study:
   - within 30 days: tetrabenazine or valbenazine
   - within 21 days: reserpine
   - within 14 days: levodopa, dopamine agonists, and monoamine oxidase inhibitors

f. Patient has received treatment with stem cells, deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation for treatment of abnormal movements or cerebral palsy since the week 15 visit of Study TV50717-CNS-30080, or the patient is not in a stable clinical condition.

g. Patient had a surgical procedure since the week 15 visit of Study TV50717-CNS-30080 or is anticipated to have a surgical procedure during the study that, in the opinion of the investigator, makes the patient unsuitable for the study.

h. Patient has a severe mental disability or an unstable or serious medical illness (eg, epilepsy) that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.

i. Patient has a QT interval corrected for heart rate (QTc) using Fridericia's formula (QTcF) value >450 msec on 12-lead ECG at screening or day 1 (whichever comes first) of this study.

j. Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, other cardiac arrhythmias, or uncompensated heart failure.

k. Patient has evidence of hepatic impairment, as indicated by the following:
   - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5× the upper limit of the normal range (ULN) at the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable

- alkaline phosphatase (ALP) or total bilirubin (Tbil) >2×ULN at the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable
- Note: Patients with Gilbert's syndrome are eligible to participate if approved by the medical monitor.
- Note: Patients with abnormalities in 2 or more of AST, ALT, ALP, and Tbil parameters that do not meet the above laboratory criteria for exclusion based on hepatic impairment must be approved for enrollment by the medical monitor.

l. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5×ULN at the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable.

m. Patient has a known allergy to any of the components of TEV-50717.

n. Patient has participated in an investigational drug or device study other than Study TV50717-CNS-30080 and received IMP/intervention within 30 days or 5 drug half-lives of day 1 of this study, whichever is longer.

o. Patient is pregnant or breastfeeding.

p. Patient has a history of or acknowledges alcohol or substance abuse.

q. Patient has a positive urine drug screen test result since the week 15 or week 16 visit of Study TV50717-CNS-30080 or at screening (as applicable) of this study (with exception of medications listed in Table 11 of Appendix H or a justified medical explanation). Any request to include a patient with a positive urine drug screen test result should be discussed with, and approved by, the medical monitor.

Statistical Considerations

Sample Size Rationale:

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.

Analysis Sets

A single analysis set is defined for this clinical study, the intent to treat (ITT) analysis set.

Intent-to-Treat Analysis Set:

The 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 reported in the database. All analyses will be based on the ITT analysis set.

Additional Analyses Sets:

Additional analysis sets may be defined in the Statistical Analysis Plan.

Analysis of Safety:

Safety analyses will be presented for the ITT analysis set. Patients that did not receive any TEV-50717 will be excluded from the summaries and presented in listings only.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events, adverse events determined by the investigator to be related to TEV-50717, serious adverse events, and adverse events causing withdrawal from the study. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Observed values and changes from day 1 in laboratory results and vital signs will be summarized descriptively.

Observed values in ECG parameters will be summarized, and counts and percentages of abnormal findings will be presented. Changes from baseline of the parent study in ECG parameters will be summarized descriptively. In addition, the number and percentage of patients with on-treatment QTcF values >450, >480, or >500 msec and change from day 1 >30 or >60 msec will be presented.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with TEV-50717.

Observed values in the children's C-SSRS will be presented for all patients.

Assessments of drug-induced parkinsonism according to the ESRS (subscales I and II), of change in behavior according to the CBCL questionnaire, and assessment of sedation according to the ESS questionnaire will be summarized descriptively.

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 clinical study report.

Analysis of Efficacy:

Descriptive statistics will be used to summarize efficacy measures.

Descriptive statistics of change-from-day 1 will utilize day 1 from the present open-label study (Study TEV-50717-30081).

The ITT analysis set will be used for all summaries, unless otherwise noted.

There is no planned interim analysis of this study. Intermediate analysis may be performed for submission of an NDA or other purposes.

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Abbreviation	Term
ADL	activities of daily living
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BoNT	botulinum neurotoxin
CaGI-I	Caregiver Global Impression of Improvement
CBCL	Child Behavior Checklist (for ages 6-18)
CDMS	clinical data management system
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CIOMS	Council for International Organizations of Medical Sciences
COPM	Canadian Occupational Performance Measure
COVID-19	coronavirus disease 2019
CP	cerebral palsy
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
CYP2D6	cytochrome P450 2D6
DCP	dyskinesia in cerebral palsy
DSM-V™	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
ESRS	Extrapyramidal Symptom Rating Scale (subscales I and II)
ESS	Epworth Sleepiness Scale (for children and adolescents)
ET	early termination
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPSP	Global Patient Safety and Pharmacovigilance
HD	Huntington's disease
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation	Term
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Response Systems
LSO	local safety officer
MAOI	monoamine oxidase inhibitor
MD-CRS	Movement Disorder-Childhood Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PEDI-CAT	Pediatric Evaluation Disability Inventory-Computer Adapted Test
PedsQL	Pediatric Quality of Life Inventory
PND	postnatal day
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RSI	reference safety information
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
Tbil	total bilirubin
TD	tardive dyskinesia
TS	Tourette syndrome
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
ULN	upper limit of the normal range
US	United States
VMAT2	vesicular monoamine transporter type 2
XML	Extensible Markup Language
α-HTBZ	alpha-dihydrotetrabenazine
β-HCG	beta-human chorionic gonadotropin
β-HTBZ	beta-dihydrotetrabenazine

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

Cerebral palsy (CP) denotes a non-progressive disturbance of brain function that usually occurs in the developing fetal or infant brain (age ≤2 years) (Rosenbaum et al 2007). It is the most common and costly form of chronic motor disability in children, with a prevalence of 2 to 4 per 1,000 live births in the United States (US), and the condition is more common in boys than in girls (CDC Data and Statistics for Cerebral Palsy 2018, Maenner et al 2016, Monbaliu et al 2017, Prevalence of Cerebral Palsy 2018). Although there have been no general studies of life expectancy in people with CP, most children affected by CP live between 30 and 70 years, depending on the severity of the condition. In general, a child with a mild case of CP usually lives longer than a child with mobility and intellectual limitations (Cerebral Palsy Life Expectancy 2018). In the US, there are about 764,000 children and adults with CP, including about 500,000 children under the age of 18 years (Prevalence of Cerebral Palsy 2018).

Prematurity is the most common cause of CP, but other causes include stroke, hypoxic ischemic injury, infection, brain malformation, and genetic abnormalities (CDC Causes and Risk Factors of Cerebral Palsy 2018; NINDS Cerebral Palsy: Hope Through Research 2019). Complications of CP may include eye movement abnormalities, communication problems, swallowing difficulty, poor weight gain, social isolation, hip dysplasia and dislocation, scoliosis, osteopenia and fractures, and pain. A variety of movement disorders are associated with CP, including spasticity, dyskinesia (dystonia, chorea, athetosis, and even ballismus), and ataxia. Many patients with CP present with mixed types of movement disorders (CDC Causes and Risk Factors of Cerebral Palsy 2018, Monbaliu et al 2017).

Dyskinesia is considered to result from an insult of non-progressive nature in the basal ganglia of the brain. Dyskinesia in cerebral palsy (DCP) is a form of CP characterized by abnormal involuntary movements of the dystonic and choreiform types in approximately 6% to 15% of patients with CP. DCP is a rare disease, and based on the above prevalence numbers of CP in the US, one could assume that approximately 30,000 to 75,000 children <18 years of age and 16,000 to 40,000 adults have DCP (Monbaliu et al 2017).

There are currently no approved treatments for DCP, which is a serious disease with an unmet medical need. Current treatment options (off-label use) to treat dystonia and chorea include tetrabenazine, dopaminergic, or gamma-aminobutyric acidergic interventions, but these show high variability in response (Monbaliu et al 2017). Botulinum neurotoxin A is also in clinical use for the treatment of spasticity and dystonia and is considered modestly effective in selected patients, but it does not meet the full treatment need. Currently, there are very few agents with novel mechanisms of action in development for movement disorders in CP.

The purpose of the study is to determine whether long-term treatment with TEV-50717 is safe, tolerable, and effective in the treatment of dyskinetic involuntary movements associated with CP.

1.1.1. Background for TEV-50717

TEV-50717 (deutetrabenazine, also known as SD-809) was initially developed to provide patients and prescribers with an effective treatment for chorea in Huntington's disease (HD) with

an improved pharmacokinetic and tolerability profile compared with tetrabenazine. TEV-50717 is a vesicular monoamine transporter type 2 (VMAT2) inhibitor structurally related to tetrabenazine, with 2 trideuteromethoxy groups instead of the 2 methoxy groups attached to the positions 9 and 10 of tetrabenazine. This deuterium placement does not change the target pharmacology, but it attenuates metabolism through cytochrome P450 2D6 (CYP2D6). Thus, this deuterium placement in TEV-50717 increases the half-life of the active metabolites relative to those of tetrabenazine, enabling reduced dosing frequency and plasma fluctuation and thus potentially improving safety and tolerability.

TEV-50717 is a VMAT2 inhibitor with the chemical name (RR,SS)-1,3,4,6,7,11b-hexahydro-9,10-di(methoxy-d3)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one. TEV-50717 tablets are 6, 9, and 12 mg, or other commercially available, dose strengths, all of which are identical in size and shape. Each strength will be a colored tablet with a marking of "SD" and the corresponding strength. The investigational medicinal product (IMP) will be supplied in 60-count tablets per bottle.

TEV-50717 was approved for the treatment of chorea associated with HD and for the treatment of tardive dyskinesia (TD) in adults on 03 April 2017 and 30 August 2017, respectively. For details, see also the US Prescribing Information (AUSTEDO USPI 2017).

1.1.2. Experience with Tetrabenazine in the Treatment of Dyskinesia in Cerebral Palsy and Other Hyperkinetic Movement Disorders in Children and Adolescents

Tetrabenazine is another VMAT2 inhibitor that presynaptically depletes monoamines, such as dopamine, serotonin, norepinephrine, and histamine, from nerve terminals (Kaur et al 2016). Although widely known among physicians treating DCP, there is limited and rather anecdotal literature on the potential efficacy of tetrabenazine on the treatment of hyperkinetic movement disorders in patients with CP of pediatric age.

Tetrabenazine has been studied in a pediatric population with a variety of hyperkinetic movement disorders. Jain et al (2006) reviewed the outcomes of 31 children at Columbia University Medical Center who were treated with tetrabenazine. Eighteen of these children had chorea, of which half had additional movement disorders, 10 had tics, and 3 had dystonia. The average duration of symptoms before treatment was 4 years, and the age of children in the study ranged from 22 months to 18 years, with a mean age of 11±4.9 years. The primary causes of the abnormal movements in these pediatric patients were CP in 2 patients; primary generalized dystonia in 2 patients; various brain injuries (intraventricular hemorrhage with developmental delay or post-hypoxic injury), genetic abnormalities with brain lesions (arteriovenous malformations with developmental delay and neurofibromatosis type I), metabolic disorders (propionic acidemia, Lesch-Nyhan syndrome, and Leigh's syndrome), immune mediated (Sydenham's chorea), medication effects (tardive dystonia or withdrawal-emergent syndrome), and unknown etiology in 5 patients. Doses of tetrabenazine ranged from 25 mg daily (0.9 mg/kg/day) to 350 mg daily (10 mg/kg/day), and the average dose was 107 mg daily (3.7 mg/kg/day). Twenty-four of these pediatric patients with hyperkinetic movement disorders had improved symptoms (14 out of 18 with chorea, 8 out of 10 with tics, and 2 out of 3 with dystonia). Adverse events and tolerability findings were present in 19 (61%) patients who had at least 1 side effect (sedation, 35%; behavioral changes, 19%; depression, 10%; nausea, 3%; and parkinsonism, 3%), and the treatment was stopped in 17 (55%) patients.

Although not related to CP, in another study, Vuong et al (2004) evaluated the safety and efficacy of tetrabenazine as a potential treatment for hyperkinetic movement disorders in 10 patients with chorea, 12 patients with dystonia, and 53 patients with tics. In this study, the doses ranged from 6.25 to 150 mg/day. The patients with chorea had approximately 90% improvement at the second visit, and those with dystonia had approximately 50% improvement at the second visit. Adverse events included dose-dependent nausea, vomiting, drowsiness, and depression.

1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics, and toxicology studies and clinical studies are provided in the following sections. More detailed information is provided in the Investigator's Brochure (IB).

1.2.1. Nonclinical Studies

The key nonclinical study findings are provided below, with details available in the IB.

1.2.1.1. Nonclinical Pharmacology

TEV-50717 is a selectively deuterium-substituted VMAT2 inhibitor structurally related to tetrabenazine. The biologically active metabolites formed from TEV-50717 (alpha-dihydrotetrabenazine [α-HTBZ] and beta-dihydrotetrabenazine [β-HTBZ]) are potent inhibitors of VMAT2 binding, with inhibition constant values of 3.8 and 22 nM, respectively, that are similar to previously reported values of their corresponding non-deuterated forms (Scherman et al 1988). Off-target binding occurs at a similar extent with deuterated and non-deuterated α-HTBZ and β-HTBZ. TEV-50717 and tetrabenazine in male rats at doses resulting in similar systemic exposure to the test articles (α-HTBZ and β-HTBZ) produced similar, expected, exaggerated central nervous system pharmacological effects. In particular, the adverse event of catalepsy, a known response in rats to drugs that reduce central nervous system dopamine concentrations (Fuenmayor and Vogt 1979), was similar in magnitude after TEV-50717 and tetrabenazine administration.

1.2.1.2. Nonclinical Pharmacokinetics and Drug Metabolism

In human liver S9, the metabolite profile of TEV-50717 overlapped with that of tetrabenazine. In a clinical comparative human [^{14}C]-absorption, distribution, metabolism, and excretion and mass-balance study, the approximately 22 metabolites of TEV-50717 were also metabolites of tetrabenazine. Thus, previous clinical experience with tetrabenazine provides predictive information about the safety of TEV-50717 and its metabolites.

Tetrabenazine, α-HTBZ, and β-HTBZ and, by extension, their deuterated forms, do not inhibit or induce cytochrome P450 (CYP) isoenzymes at clinically relevant concentrations (Xenazine Prescribing Information 2017). M1, a minor metabolite that may circulate in greater concentrations as a metabolite of TEV-50717 as compared to tetrabenazine, is neither an inhibitor of major CYP isozymes or transporters nor an inducer of CYP isozymes. M4, a major metabolite of tetrabenazine and TEV-50717, is neither an inhibitor of major CYP isozymes or transporters nor an inducer of CYP isozymes.

1.2.1.3. Toxicology

General and Reproductive Adult Toxicology: Oral administration of TEV-50717 in rats reduced body weight gain, increased mammary hyperplasia, and produced estrous cycle changes, all of which occurred with tetrabenazine at doses that produced similar systemic exposures to test articles and metabolites. Mammary and estrus effects are likely consequences of reduced central dopamine and subsequent increased prolactin, consistent with information in the Xenazine® (tetrabenazine) label. Oral administration of TEV-50717 in pregnant rats did not produce test article-related embryofetal toxicities, even at doses that led to reduced body weight gain in dams. Oral administration of metabolite M1 to pregnant rats from gestational days 6 to 17 produced no test article-related maternal or fetal toxicities.

Genetic Toxicology: TEV-50717 and its α-HTBZ and β-HTBZ metabolites were negative in in vitro studies for mutagenicity (bacterial reverse mutation or the Ames test) and for chromosomal structural aberrations in human peripheral blood lymphocytes. Oral doses of TEV-50717 were negative for inducing micronuclei in the bone marrow of treated mice.

Juvenile Toxicology: The effects of TEV-50717 on juvenile development was assessed in male and female rats with oral dosing from weaning (postnatal day [PND] 21) to PND 71, similar to human dosing from year 2 through early adolescence and overlapping with TEV-50717 oral dosing in a general adult toxicology study. The effects of M1 was assessed in male and female juvenile rats from PND 25 to PND 70 with a recovery phase and postdosing reproductive assessment.

TEV-50717 produced no test article-related effects on learning and memory functions, on histopathology assessments, on reproductive capacity (male and female fertility and estrus cyclicity), or on intrauterine survival of embryos from matings during recovery from test article administration. Adversely reduced body weight gain and adverse clinical observation of tremors and in-cage hyperactivity were all noted in previous studies with adult rats; these effects have not predicted adult clinical intolerance to TEV-50717. The highest dose level of M1 (50 mg/kg/day) produced no test article-related toxicities (clinical observations, changes in body weight gain, clinical pathology, histopathology, ophthalmology, and performance in learning and memory tests).

1.2.2. Clinical Studies

The clinical development plan for TEV-50717 to date includes the following:

- fourteen completed Phase 1 studies in healthy adult volunteers
- one completed Phase 3 pivotal study for the treatment of chorea associated with HD
- one completed Phase 3 long-term safety study in patients with HD
- two completed pivotal Phase 2/3 and Phase 3 studies in patients with TD
- one completed Phase 3 long-term safety study in patients with TD
- one completed Phase 1b study in patients with Tourette syndrome (TS)
- two completed pivotal studies in patients with TS
- one terminated Phase 3 long-term safety study in patients with TS

- one ongoing Phase 3 efficacy and safety study in patients with DCP

Further details may be found in the IB.

1.2.2.1. Clinical Pharmacology Studies

Fourteen Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers. In addition, sparse pharmacokinetic sampling was included in the Phase 3 studies in patients with HD and TD where the population pharmacokinetic analyses including these data have been performed to extensively evaluate both the pharmacokinetics and pharmacokinetic-pharmacodynamic relationship of TEV-50717. A summary of the clinical pharmacology findings is provided in the IB.

Pharmacometric analyses of the active metabolites of TEV-50717 based on the Phase 1 clinical pharmacology studies in healthy adult volunteers were performed to support dose selection and pharmacokinetic characterization in a pediatric population. Subsequently, a further pharmacometric analysis of active metabolites following administration of TEV-50717 to adolescent patients with TS with tics (Study SD-809-C-17) was completed. The results of these analyses are described in Section 1.2.2.3.

1.2.2.2. Clinical Safety and Efficacy Studies

The safety profile of TEV-50717 has been characterized to date in healthy volunteers, as well as in adult patients with chorea associated with HD and TD (as detailed in the IB) and in children and adolescents with TS. Study SD-809-C-17 also evaluated the safety of TEV-50717 in adolescent patients with TS. Results of the safety analyses indicate that treatment with TEV-50717 at doses up to 36 mg daily given in 2 divided doses is generally safe and well tolerated for up to 8 weeks in patients with TS. No serious treatment-emergent adverse events or severe treatment-emergent adverse events occurred in this study. The most frequently observed treatment-emergent adverse events during the entire treatment period were fatigue and headache, each reported in 4/23 (17.4%) patients, followed by irritability, which was reported in 3/23 (13.0%) patients.

Studies TV50717-CNS-30046 and TV50717-CNS-30060 evaluated children and adolescent patients with tics associated with TS. Neither study met the primary efficacy endpoint. In both studies, TEV-50717 was generally safe and well tolerated. No deaths occurred in either study. One patient had 2 serious adverse events. There were no trends in changes from baseline in serum laboratory, vital signs, ECG, and physical and neurological parameters. There was no evidence of a new safety signal in pediatric patients with TS treated with TEV-50717 in comparison to the known safety profile of this drug in adult patients with HD or TD.

The open-label, long-term Study TV50717-CNS-30047 evaluated children and adolescent patients with tics associated with TS. Treatment with TEV-50717 through 54 weeks resulted in improvement of tics. The safety profile observed in pediatric patients with TS receiving long-term treatment with TEV-50717 was generally comparable to the known safety profile of this drug in adult patients with HD or TD, with the exception of the adverse event of weight gain.

There were no clinically meaningful trends in mean changes from baseline for any clinical laboratory variable or any other observations related to safety.

The ongoing Study TV50717-CNS-30080 is the first study to assess the safety, tolerability, and efficacy of TEV-50717 in patients with DCP. This study (Study TV50717-CNS-30081) is being conducted to provide more details on the long-term safety and efficacy of treatment with TEV-50717 in patients with DCP.

1.2.2.3. Pharmacometric Analysis of TEV-50717 Active Metabolites to Support Dose Selection and Pharmacokinetic Characterization in a Pediatric Population

Population pharmacokinetic modeling of the TEV-50717 active metabolites α-HTBZ and β-HTBZ has been performed throughout the clinical development program. Based on sequential pharmacokinetic sampling data obtained in healthy volunteers in the Phase 1 program, a structural population pharmacokinetic model was developed to guide dose selection for HD patients with chorea (Study SD-809-CLN-076) and subsequently optimized to better describe the absorption/bioconversion profile of α-HTBZ and β-HTBZ (Study SD-809-CLN-077).

Employing the structural model defined in Study SD-809-CLN-077, sequential and sparse pharmacokinetic sampling data obtained from Study SD-809-C-17 were combined with the Phase 1 data employed in Study SD-809-CLN-077 to estimate the total (α+β)-HTBZ exposure in adolescent patients (age 12 through 18 years) with TS and to simulate exposure in adolescent and pediatric patients (age 6 through 11 years) with and without concomitant CYP2D6 impairment (genetic or because of concomitant use of a strong CYP2D6 inhibitor) across a range of doses (Appendix H). Population model parameters were re-estimated for the combined Phase 1 and adolescent data obtained from patients in Study SD-809-C-17. The model was used to simulate total (α+β)-HTBZ exposures across a range of body weights corresponding to a pediatric and adolescent population according to the Centers for Disease Control growth charts.

This analysis indicated that exposure to total (α+β)-HTBZ is influenced by body weight, and a reduction in dose for pediatric and adolescent patients weighing <40 kg is necessary in order to provide comparable exposure to doses up to 48 mg/day in adults, a level previously demonstrated to be safe and well tolerated in treated patients with chorea associated with HD.

This analysis provides the basis for the dosing recommendations in Section 5.1.1.1.

1.3. Known and Potential Benefits and Risks to Patients

1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)

Additional information regarding benefits and risks to patients may be found in the current IB and in the US prescribing information for AUSTEDO® (deutetrabenazine).

1.3.1.1. Benefits of TEV-50717

Although the efficacy of TEV-50717 in patients with DCP has not yet been established, TEV-50717 has already provided evidence for safe and effective use in 2 hyperkinetic movement disorders, namely chorea in HD and TD.

1.3.1.2. Potential Risks of TEV-50717

The following information is based on clinical trial experience with TEV-50717 and the US prescribing information for Xenazine (tetrabenazine) and Austedo (deutetrabenazine):

- TEV-50717 is contraindicated in patients with HD who are actively suicidal or in patients with untreated or inadequately treated depression.
- TEV-50717 is contraindicated in patients with impaired hepatic function.
- TEV-50717 is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). TEV-50717 should not be used in combination with a MAOI or within a minimum of 14 days of discontinuing therapy with a MAOI.
- TEV-50717 is contraindicated in patients taking reserpine. At least 21 days should elapse after stopping reserpine before starting TEV-50717.
- TEV-50717 is contraindicated in patients taking tetrabenazine or valbenazine. At least 30 days should elapse after stopping tetrabenazine or valbenazine before starting TEV-50717.

Additional information regarding each potential issue may be found in the current IB.

1.3.2. Overall Benefit and Risk Assessment for This Study

There are currently no approved treatments for DCP, which is a serious disease with an unmet medical need. Also, there is a significant need to identify effective treatments for DCP. The results from studies in other study populations, such as patients with TS or HD, demonstrated no signal on safety scales, vital signs, laboratory parameters, or 12-lead electrocardiograms (ECGs). The rates for TEV-50717 and placebo were similar for overall adverse events, neurologic and psychiatric adverse events, as well as dose reduction or dose suspension for adverse events (see the IB for details).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are the following:

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 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
The **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 (activities of daily living, caregiver completed, content-balanced version) • UHDRS-TMC (centrally read) • UHDRS-TMD (centrally read) • UHDRS-TMS (physician rated) • 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; 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.

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

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 the TV50717-CNS-30080 study. Any patient who cannot enroll within this timeframe, for any justified reason, must be discussed and pre-approved by the medical monitor prior to enrolling the patient. 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. 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.

For the purposes of this protocol, a caregiver is defined as an adult, who is familiar with the patient and responsible for daily care, enabling that person to effectively complete the protocol requirements. The caregiver accompanies the patient to the visits and provides input to the relevant scales as required by the protocol.

For patients who are minors, the caregiver is typically a parent or legally acceptable representative. In some countries, an adult (such as grandparent or nurse) may be appointed by the parent or legally acceptable representative (as per local regulations and laws) and would take over this responsibility as caregiver. The parent or legally acceptable representative only has to sign the parent/legally acceptable representative informed consent form (ICF) and not the caregiver ICF.

For adult patients, a caregiver must be appointed by the patient. The caregiver can be the parent or other adult as appropriate and according to local laws and regulations.

For patients who are minors, certain responsibilities in the protocol can only be completed by the parent/legally acceptable representative, ie, informed consent, withdrawal of consent, requests for discontinuation of IMP, or withdrawal from the study for any reason. To further clarify, the caregiver is not allowed to make decisions on the child's health, or where "parent/legally acceptable representative" is specifically indicated in the protocol.

Site-administered scales include the Movement Disorder-Childhood Rating Scale (MD-CRS) parts I and II (physician rated, with video recording), Caregiver Global Impression of Improvement (CaGI-I), Clinical Global Impression of Improvement (CGI-I), Clinical Global Impression of Severity (CGI-S), Pediatric Evaluation Disability Inventory-Computer Adapted

Test (PEDI-CAT), Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS), Unified Huntington's Disease Rating Scale-Total Maximal Chorea (UHDRS-TMC), Unified Huntington's Disease Rating Scale-Total Maximal Dystonia (UHDRS-TMD), Canadian Occupational Performance Measure (COPM), children's Columbia-Suicide Severity Rating Scale (C-SSRS), Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II, Child Behavior Checklist (CBCL) for ages 6 to 18 years, and Epworth Sleepiness Scale (for children and adolescents) (ESS) questionnaire. Children 13 years of age and under must be interviewed in conjunction with the caregiver. For children over 13 years of age, questions should be directed to the child; however, caregiver involvement is strongly encouraged to add relevant information.

In the study period descriptions below, "week X" refers to the end of that week, which coincides with the study visit, unless stated otherwise. Some dose changes will occur at the start of a week, rather than at the end of a week, and will be indicated as such.

Patients can either enroll in the study at the week 16 visit of Study TV50717-CNS-30080 or up to 4 weeks 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 (Figure 2).

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, electrocardiogram (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.

In addition, the following applies for day 1 baseline assessments for this study:

- clinically significant laboratory abnormalities identified at week 15 in Study TV50717-CNS-30080 are to be repeated at week 16 of the parent study for eligibility in Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. Any abnormalities which are listed in the inclusion/exclusion criteria must be discussed with the medical monitor prior to patient enrollment into the study.
- Urine drug screen is performed at week 16 in study TV50717-CNS-30080 and will serve as day 1 baseline values in this study.
- 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.

- weight is performed at week 16 in Study TV50717-CNS-30080 and height is performed at week 15 in study TV50717-CNS-30080; these assessments will serve as day 1 baseline values in this study.
- vital signs (respiratory rate and body temperature) are performed at week 16 in 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, these assessments will serve as day 1 baseline values in this study. Otherwise, these assessments will be performed at day 1.
- physical and neurological examinations are performed at week 15 (and week 16, if applicable) in Study TV50717-CNS-30080. The findings from the last assessment taken will serve as day 1 baseline values in this study.
- ECG is to be performed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study.
- medical and psychiatric history are to be assessed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study.
- COPM (an assessment included only in Study TV50717-CNS-30081) will also be performed at day 1.

At the investigator's discretion, abnormal findings can be discussed with the medical monitor.

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 4, 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 4. 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.

For patients who enroll in the study between 2 and ≤4 weeks after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.

Titration period (7 weeks): Because the patients from parent Study TV50717-CNS-30080 have discontinued TEV-50717 treatment for at least 1 week at completion of the parent study or received placebo in the parent study, 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 (Table 6). 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 TEV-50717 tablets cannot be crushed or split but should be swallowed whole; the TEV-50717 tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. The titration scheme and maximum dose will be determined by body weight at day 1 and CYP2D6 impairment status, as shown in Table 6 and Table 7, respectively. 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, as shown in Table 7.

Patients and their caregiver will interact weekly with the clinical research staff, either by telephone contact (with non-recording live video) or in-clinic visits from week 1 through week 7 of the titration period, in order to evaluate safety and establish a dose of TEV-50717 that optimally reduces dyskinesia (as indicated by a reduction in the CGI-I) and is well tolerated (optimal dose). The telephone contacts to the patient will be supported by live video stream, without recording, to provide visual confirmation to the investigator of the verbal information provided by the patient or caregiver. Safety evaluations during the titration period include assessment of vital signs, monitoring for adverse events and concomitant medications, 12-lead ECGs, identifying patients at risk for suicide, assessment of drug-induced parkinsonism according to the ESRS (subscales I and II), assessment of change in behavior according to the CBCL questionnaire, and assessment of sedation according to the 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.

The dose of TEV-50717 should be increased to reach a clinically meaningful reduction in dyskinesia, as indicated by a reduction in the CGI-I (see Table 6). The dose of TEV-50717 should not be increased further if either of the following occurs:

- the patient experiences a “clinically significant” adverse event (defined as an adverse event that is related to TEV-50717 and is either moderate or severe in intensity or meets the criteria for a serious adverse event), OR
- the maximum allowable dose is reached based on the patient’s weight and CYP2D6 impairment status at day 1. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor.

Dose adjustments can be made up to and including the week 7 in-clinic visit. If an optimal dose is reached before the week 7 in-clinic visit, the dose of TEV-50717 should not be increased further, but the patient should continue on that dose for the remainder of the titration period. If a patient experiences a “clinically significant” adverse event attributable to TEV-50717, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible. If the determination that a patient requires a dose reduction or suspension is made during a telephone contact, an unscheduled clinic visit should be conducted as soon as practicable thereafter.

Dose adjustments should be made based on all available information, including the patient and caregiver reports of adverse events and dyskinesia reduction, the clinical assessment of safety and efficacy by the investigator, and the information from rating scales.

All IMP adjustments are made only after a remote or in-clinic visit; if the dose is escalated, the dose escalation will occur with the next morning's dose.

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 (Table 6 and Table 7). As during titration, dose adjustments should be made based on all available information. Dose reductions of TEV-50717 or suspensions of patients for adverse events or tolerability findings are allowed.

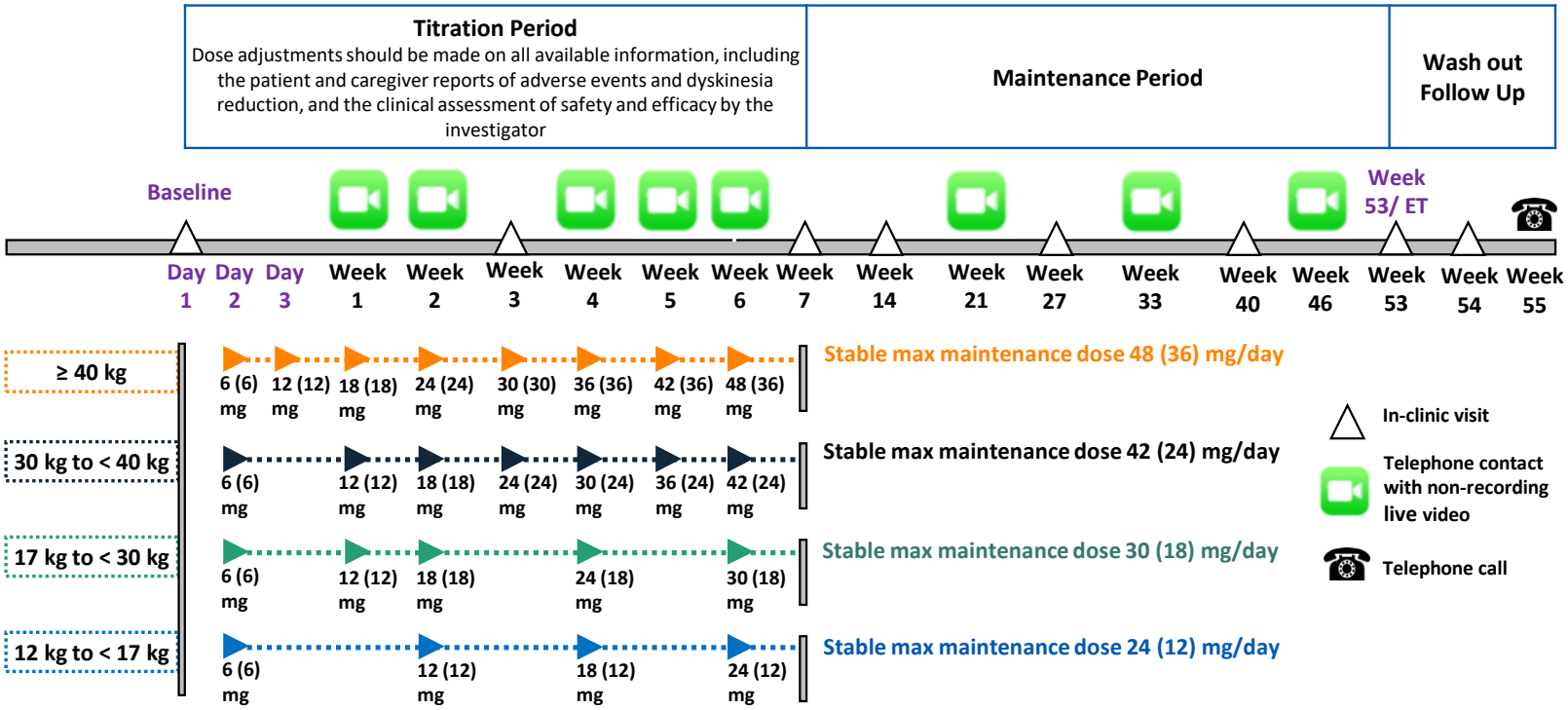
During the maintenance period, in-person (in-clinic) study visits will be scheduled at weeks 14, 27, 40, and 53 for assessments of safety and efficacy, and telephone contacts (with non-recording live video) will be scheduled for weeks 21, 33, and 46 in order to assess adverse events and dyskinesia. At week 53/early termination (ET), patients will undergo a complete evaluation, including vital signs and weight, physical and neurological examination, height measurement, 12-lead ECG, safety laboratory testing, urine drug screen, and beta-human chorionic gonadotropin (β-HCG) test, when applicable, as well as the MD-CRS parts I and II, CaGI-I, CGI-I, CGI-S, PEDI-CAT, UHDRS-TMS, UHDRS-TMC, UHDRS-TMD, COPM, children's C-SSRS assessments, ESRS (subscales I and II), CBCL, and ESS.

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 4 and for the titration, maintenance, and follow-up periods in Table 5. 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.

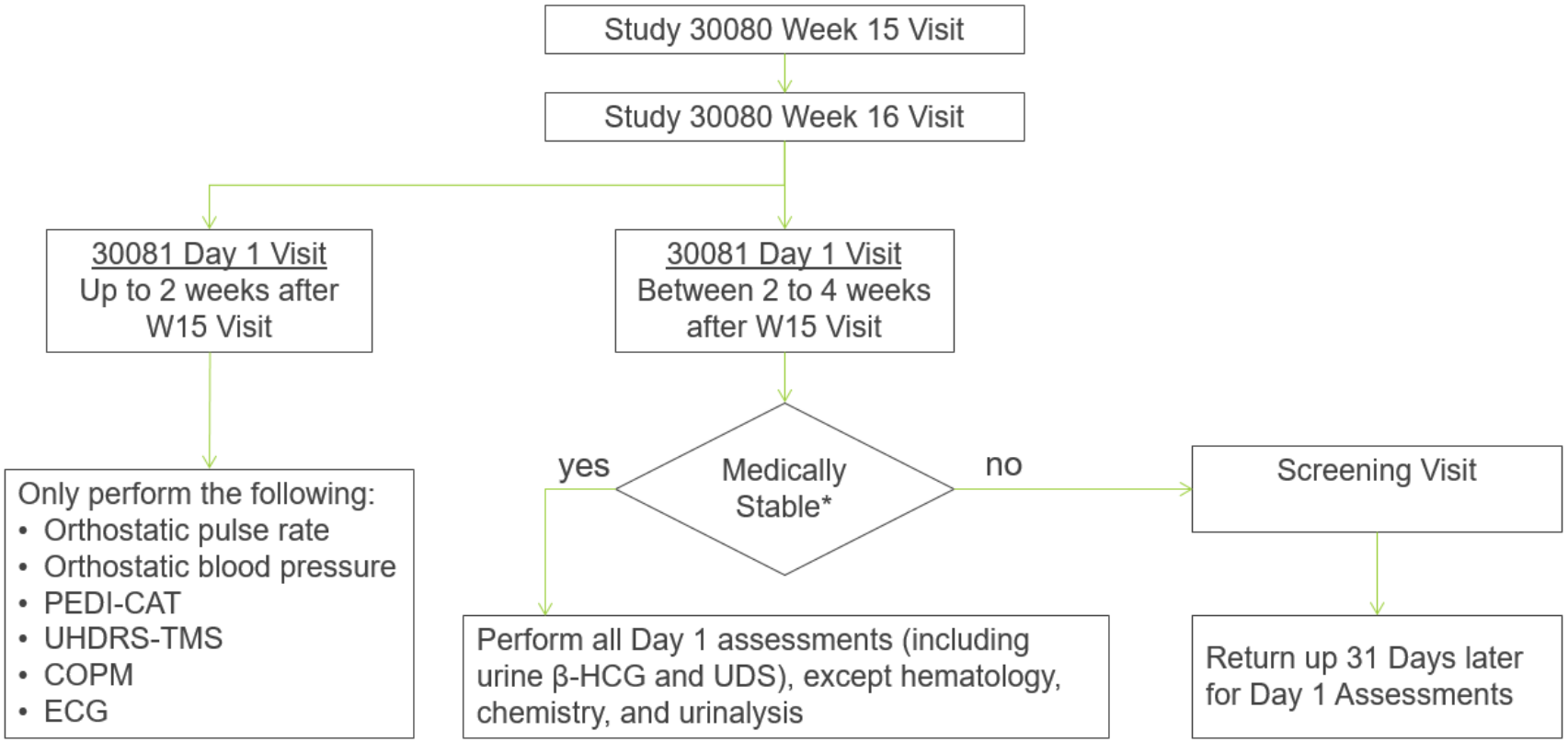
For coronavirus disease 2019 (COVID-19) updates, refer to Appendix M.

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.

3.2. Planned Number of Patients and Regions

Approximately 45 subjects who have completed parent Study TV50717-CNS-30080 are planned for enrollment into this study.

This study is planned to be conducted in approximately 35 investigational centers in North America, Europe, and Asia.

3.3. Justification for Study Design and Selection of Population

Currently, there is no approved treatment available for DCP. DCP is a hyperkinetic motor impairment due to a non-progressive disturbance of brain function that occurs in the developing fetal or infant brain, generally before the age of 2 years. DCP has a major debilitating impact on the ability of the child with CP to further develop motor skills. The available treatment options address some of the manifestations of DCP.

The study population will include pediatric and adolescent patients (6 through 18 years of age at the time when they enrolled in the parent study [Study TV50717-CNS-30080]), ie, 6 through 20 years of age when they enroll in TV50717-CNS-30081 study, with DCP with predominant choreiform movement disorder, who have had non-progressive CP symptoms since infancy (≤2 years of age), and have completed Study TV50717-CNS-30080. The diagnosis of DCP is based on the Surveillance of Cerebral Palsy in Europe criteria (Cans 2000). "Predominant" in this instance indicates that the choreiform movement disorder is the main cause of impairment or distress.

Study TV50717-CNS-30081 uses the same versions of scales as in the parent study, to maintain consistency of evaluations between these studies. As such, Study TV50717-CNS-30081 includes some scales that are designated for patients up to 18 years old, although potentially some patients who entered the parent study at age 18 will now be over 18 years old in this extension study.

Consequently, the open-label study design was chosen for this Phase 3 study to determine whether long-term treatment with TEV-50717 results in favorable safety, tolerability, and efficacy findings in children and adolescents with DCP.

3.4. Stopping Rules for the Study

During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5), as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor may terminate the study in the event of the following:

- new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the IMP

If the study will be stopped, the patients who are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.3).

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented for screening and/or day 1 in Table 4 and for the titration, maintenance, and follow-up periods in Table 5. During a visit, study procedures and assessments should be performed in the order specified in the study manual.

Detailed by-visit information is provided in the sections following the table. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments) and Section 7 (safety assessments). Study procedures and assessments by visit are listed in Appendix C.

For COVID-19 updates, refer to Appendix M.

Table 4: 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 5: 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		

	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**	
CGI-S (global, physician rated)[o]								X		X		X		X	X		
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[u]	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.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by Teva (Appendix D).

Standard of care for treatment of CP should continue throughout the study, with some possible restrictions, for example, as outlined in Section 5.5. Standard of care could include any possible rehabilitation service(s), such as physiotherapy, occupational therapy, or sensory integration of the patient.

4.1. Patient Inclusion Criteria

Patients who meet the criteria below are eligible to be included in the study.

a. Patient has completed week 16 of Study TV50717-CNS-30080.

b. Patient weighs at least 12 kg (26 lbs) on day 1 of this study.

c. Patient is able to swallow TEV-50717 tablet whole.

d. Patient and caregiver are willing to adhere to TEV-50717 regimen and comply with all study procedures.

e. Patient is in good general health, as indicated by medical and psychiatric history and physical and neurological examination.

f. In the investigator's opinion, the patient and/or caregiver has the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed.

g. For a patient who is a minor, the parent(s)/legally acceptable representative(s) provides written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide written informed consent (in accordance with local regulations), and the legally acceptable representative will sign, if needed.

   In this study, eligible patients with dyskinetic cerebral palsy may have some degree of mental, motor, and/or communication (eg, speech, writing, etc.) limitations or disabilities. The patient may not be able to read the assent/consent form. Some patients may only be able to provide a limited assent/consent (for instance, by verbalizations or gestures). The investigator will determine the suitability of enrolling such patients in this study and will follow the local regulation to obtain the relevant consent/assent.

h. A caregiver provides written informed consent after being assigned the role by an adult patient or if this role is delegated by the parent/legally acceptable representative of a patient who is a minor.

i. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β-HCG test on day 1 or are sterile. Definitions of sterile, premenarchal, and postmenarchal are given in Appendix F.

j. Females who are postmenarchal or ≥12 years of age whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at day 1) and for 30 days after last dose of TEV-50717. Further details are included in Appendix F.

4.2. Patient Exclusion Criteria

Patients will not be randomized/enrolled in this study if they meet any of the following criteria:

a. Patient has clinically significant depression at screening or day 1 of this study.
   - Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening or day 1 (whichever comes first) and anticipated to remain stable (dose and frequency) within the study duration.

b. Patient has a history of suicidal intent or related behaviors based on medical or psychiatric history or the C-SSRS at screening visit, if performed, or at the day 1 visit, as applicable according to the patient's age:
   - intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence, at the time of suicidal thought
   - suicidal preparatory acts or behavior

c. Patient has a history of a previous actual, interrupted, or aborted suicide attempt based on medical or psychiatric history or the C-SSRS at screening visit, if performed, or at the day 1 visit, as applicable according to the patient's age.

d. Patient has a first-degree relative who has completed suicide.

e. Patient has received any of the following concomitant medications within the specified exclusionary windows from screening or day 1 (whichever comes first) of this study:
   - within 30 days: tetrabenazine or valbenazine
   - within 21 days: reserpine
   - within 14 days: levodopa, dopamine agonists, and monoamine oxidase inhibitors

f. Patient has received treatment with stem cells, deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation for treatment of abnormal movements or CP since the week 15 visit of Study TV50717-CNS-30080, or the patient is not in a stable clinical condition.

g. Patient had a surgical procedure since the week 15 visit of Study TV50717-CNS-30080 or is anticipated to have a surgical procedure during the study that, in the opinion of the investigator, makes the patient unsuitable for the study.

h. Patient has a severe mental disability or an unstable or serious medical illness (eg, epilepsy) that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.

i. Patient has a QT interval (QTc) corrected for heart rate using Fridericia's formula (QTcF) value >450 msec on 12-lead ECG at screening or day 1 (whichever comes first) of this study.

j. Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, other cardiac arrhythmias, or uncompensated heart failure.

k. Patient has evidence of hepatic impairment, as indicated by the following:

- aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5× the upper limit of the normal range (ULN) at the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable
- alkaline phosphatase (ALP) or total bilirubin (Tbil) >2×ULN at the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable
- Note: Patients with Gilbert's syndrome are eligible to participate if approved by the medical monitor.
- Note: Patients with abnormalities in 2 or more of AST, ALT, ALP, and Tbil parameters that do not meet the above laboratory criteria for exclusion based on hepatic impairment must be approved for enrollment by the medical monitor.

l. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5×ULN at the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable.

m. Patient has a known allergy to any of the components of TEV-50717.

n. Patient has participated in an investigational drug or device study other than Study TV50717-CNS-30080 and received IMP/intervention within 30 days or 5 drug half-lives of day 1 of this study, whichever is longer.

o. Patient is pregnant or breastfeeding.

p. Patient has a history of or acknowledges alcohol or substance abuse.

q. Patient has a positive urine drug screen test result since the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening (as applicable) of this study (with exception of medications listed in Table 11 of Appendix H or a justified medical explanation). Any request to include a patient with a positive urine drug screen test result should be discussed with, and approved by, the medical monitor.

4.3. Withdrawal Criteria and Procedures for the Patient

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the IMP at any time. The investigator also has the right to withdraw a patient from the IMP in the event of intercurrent illness, adverse events, pregnancy (see Section 7.3), or change in concomitant treatment (see Appendix H); patient engages in alcohol or other substance abuse; patient or parent(s)/legally acceptable representative withdraws consent or requests discontinuation from the IMP; the sponsor requests withdrawal of the patient or other reasons concerning the health or well-being of the patient; or in the event of lack of cooperation.

If a patient experiences signs of suicidal ideation or behavior (Section 7.10), the investigator should consult with the medical monitor to determine whether the patient should continue in the study. If a patient reports any suicidal behavior that is an actual attempt as assessed in the children's C-SSRS, the patient will be evaluated immediately by the investigator, referred for psychiatric evaluation, and terminated from the study.

Patients are expected to participate in this study for its entire duration and perform the scheduled visits and procedures.

Patients will be discontinued from the study for the following situations:

- Laboratory evidence of diminished hepatic function, defined as an AST or ALT >2.5×ULN and ALP or total bilirubin >2×ULN
- Patient develops neuroleptic malignant syndrome

If a post-treatment QTcF value >500 msec or change from screening or day 1 >60 msec is found, the investigator should repeat the ECG assessment twice and then compare the last pre-treatment QTcF value to the average of the 3 post-treatment QTcF values. TEV-50717 must be stopped for any confirmed post-treatment QTcF average value >500 msec or average increase from screening or day 1 >60 msec. In addition, a patient may be withdrawn from the study as described in Section 3.4, Section 3.5, and Appendix C.

Should a patient decide to withdraw after administration of TEV-50717, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given as to why the patient is withdrawing or being withdrawn from TEV-50717.

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 ET visit; evaluations will be as described for the week 55 visit.

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.

The reason for and date of withdrawal from TEV-50717 and the reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed to the case report form (CRF). If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to TEV-50717 or study procedure is made). The specific event or test result must be recorded on the source documentation and transcribed to the CRF.

See Appendix G for information regarding how the study will define and address lost to follow-up patients to help limit the amount and impact of missing data.

For COVID-19 updates, refer to Appendix M.

4.4. Replacement of Patients

A patient who is enrolled but does not complete the treatment period (from day 1 to week 53/ET) will not be replaced.

4.5. Rescreening

A patient who is screened but not enrolled (eg, because inclusion criteria were not met, exclusion criteria were met, or enrollment did not occur within the specified time) may be considered for rescreening 1 time if there is a change in the patient's medical background or other relevant change. (Note: the medical monitor should approve rescreening after review of the enabling reasons.)

Patients may have individual parameters retested at the discretion of both the investigator and the sponsor.

If the patient is rescreened, an ICF will need to be re-signed.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are subsequently not enrolled in the study. Minimal information includes, but is not limited to, demography, screening failure details, eligibility criteria, and any serious adverse events.

5. TREATMENTS

5.1. Investigational Medicinal Products Used in the Study

IMP is defined as the test IMP. There is no reference IMP or placebo IMP in this study.

5.1.1. Test Investigational Medicinal Product

Test IMP (TEV-50717 [deutetrabenazine, previously SD-809]) will be administered as oral tablets with food (eg, a snack) and should not be taken on an empty stomach. TEV-50717 is coated with a polymer coating to aid in swallowing. TEV-50717 tablets have been manufactured according to current Good Manufacturing Practice (GMP) regulations. TEV-50717 tablets will be supplied as 6-, 9-, and 12-mg, or other commercially available, dose strengths, by bottle and labeled according to applicable regulatory guidelines. Each bottle pack (60-count tablets per bottle) will contain a sufficient supply of drug until the next specified visit/telephone contact, plus overage to account for potential delays in study visits.

Additional details may be found in Table 8, the IB for TEV-50717, and the Prescribing Information for TEV-50717.

5.1.1.1. Starting Dose and Dose Levels

TEV-50717 will be administered as oral tablets at a starting dose of 6 mg once daily with food (eg, a snack) and should not be taken on an empty stomach. Titration schemes based on body weight at day 1 are shown in Table 6. The maximum daily dose is determined by body weight at day 1 and CYP2D6 impairment status (see Table 7). Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor.

TEV-50717 oral tablets are 6, 9, and 12 mg, or other commercially available, dose strengths. Each dose strength will have a marking corresponding to the dose strength on the label. TEV-50717 will be supplied as 60-count tablets per bottle. Each dose strength will be a colored tablet with a marking of “SD” and the corresponding strength.

5.1.1.2. Dose Modification and Dose Stratification

All IMP adjustments are made only after a remote or in-clinic visit; if the dose is escalated, the dose escalation will occur with the next morning’s dose.

If a patient experiences a “clinically significant” adverse event that is attributed to TEV-50717, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible. At the end of the titration period, the patient’s initial dose will be established for the maintenance period. 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 (Table 6 and Table 7). As during titration, dose adjustments should be made based on all available information. The dose of TEV-50717 may be reduced or suspended if a patient experiences an adverse event or tolerability finding during the maintenance period and the investigator believes a dose reduction or suspension is warranted.

TEV-50717 will be administered as follows:

- TEV-50717 cannot be crushed or split but should be swallowed whole; the TEV-50717 tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. Patients may be offered the optional use of a Medi+Straw®, which is a commercially available straw that can assist patients to overcome their swallowing difficulties.
- Dosing and titration will be based on body weight at the day 1 visit and CYP2D6 impairment status, as shown in Table 6 and Table 7, respectively.
- The starting dose is 6 mg in all patients. 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. If a patient misses a dose, and it is within 6 hours of the next dose, the missed dose should be skipped. If a patient is on the 6 mg once daily dose (12 kg to <17 kg; 26 lbs to <37 lbs) and experiences somnolence while taking the 6-mg dose in the morning, he/she may switch to taking it as an evening dose for the rest of the days up to day 14.
- 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.
- 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.
- 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.
- At an in-clinic visit, a dose reduction, if required, should be made to the previously tolerated dose level. **If more than 1 dose reduction is required for an adverse event, the medical monitor should be notified.**
- During the titration period, the dose of TEV-50717 should be adjusted according to Table 6 to identify a dose level that optimally reduces dyskinesia (as determined by the investigator, as indicated by a reduction in the CGI-I) and is well-tolerated. Dose adjustments should ONLY take place after a telephone or in-clinic visit.

For COVID-19 updates, refer to Appendix M.

Table 6: Maximum Daily Dose of TEV-50717 by Week and Weight Category on Day 1 for Titration at Study Initiation

Study time period	Daily dose[a, b]			
	12 kg to <17 kg (26 lbs to <37 lbs)	**17 kg to <30 kg (37 lbs to <66 lbs)**	**30 kg to <40 kg (66 lbs to <88 lbs)**	**≥40 kg (≥88 lbs)**
Day 2 **(first dose in morning)**	6 mg	6 mg	6 mg	6 mg
Week 1	6 mg	6 mg	6 mg	12 mg[c]
Week 2	6 mg	12 mg	12 mg	18 mg
Week 3	12 mg[d]	18 mg	18 mg	24 mg
Week 4	12 mg[d]	18 mg[d]	24 mg[d]	30 mg
Week 5	18 mg[d]	24 mg[d]	30 mg[d]	36 mg[d]
Week 6	18 mg[d]	24 mg[d]	36 mg[d]	42 mg[d]
Week 7	24 mg[d]	30 mg[d]	42 mg[d]	48 mg[d]

[a] All IMP adjustments are made only after a remote or in-clinic visit; if the dose is escalated, the dose escalation will occur with the next morning's dose. Dose adjustments should ONLY take place after a telephone or in-clinic visit.
[b] Dose increases may not occur more frequently than every 5 days, except for patients ≥40 kg/88 lbs. For patients ≥40 kg/88 lbs, the first dose increase should be performed in an interval less than 5 days, only once, on day 3. Refer to Table 5 for the exact visit windows at each weekly titration visit.
[c] Patients in this weight category will receive the 6 mg once-daily dose in the morning on day 2, followed by twice daily administration of 6 mg starting on day 3.
[d] For those taking strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, and bupropion, the maximum daily dose for patients ≥40 kg is 36 mg/day, that for 30 to <40 kg is 24 mg/day, that for 17 to <30 kg is 18 mg/day, and that for 12 to <17 kg is 12 mg/day (see Table 7).
CYP2D6=cytochrome P450 2D6.

Table 7: Maximum Daily Dose of TEV-50717 by CYP2D6 Impairment Status

Weight category	Maximum daily dose in the absence of CYP2D6 impairment	Maximum daily dose in the presence of CYP2D6 impairment
12 kg to <17 kg (26 lbs to <37 lbs)	24 mg	12 mg
17 kg to <30 kg (37 lbs to <66 lbs)	30 mg	18 mg
30 kg to <40 kg (66 lbs to <88 lbs)	42 mg	24 mg
≥40 kg (≥88 lbs)	48 mg	36 mg

CYP2D6=cytochrome P450 2D6.
Note: Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor. Strong CYP2D6 inhibitors include paroxetine, fluoxetine, and bupropion.

Table 8: Investigational Medicinal Products Used in the Study

IMP Name	**TEV-50717 Test IMP**
Trade name and INN, if applicable, or company-assigned number	TEV-50717 (SD-809, AUSTEDO®, deutetrabenazine)
Formulation	Modified release solid oral dosage form (tablet with film coating)
Unit dose strength(s)/Dosage level(s)	TEV-50717 tablets are 6, 9, and 12 mg, or other commercially available, dose strengths, all of which are identical in size and shape. Each strength will be a colored tablet with a marking of "SD" and the corresponding strength. Test IMP will be supplied in 60-count tablets per bottle.
Route of Administration	Oral
Packaging	Test IMP will be provided in bottles.
Manufacturer	Norwich Pharmaceuticals Inc., New York, United States (Referenced as NPI or Norwich) 6826 State Highway 12 Norwich, NY 13815 Anesta, LLC Wiley Post Way Salt Lake City, UT 84116
Storage conditions[a]	Stored at controlled room temperature, 20°C-25°C (68°F-77°F)

IMP=Investigational Medicinal Product; INN=International Nonproprietary Name.
[a] For additional information related to IMP storage conditions, please refer to the Pharmacy Manual.

5.2. Preparation, Handling, Labeling, Storage, and Accountability for IMPs

For COVID-19 updates, refer to Appendix M.

5.2.1. Storage and Security

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TEV-50717 received and any discrepancies are reported and resolved before use of TEV-50717.

TEV-50717 must be stored at a controlled room temperature, 20ºC to 25ºC (68ºF to 77ºF), in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff. For additional information related to IMP storage conditions, please refer to the Pharmacy Manual.

5.2.2. Labeling

Supplies of TEV-50717 will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

5.2.3. Accountability

Each TEV-50717 shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of TEV-50717 and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive TEV-50717 and only authorized staff at the investigational center may supply or administer TEV-50717. All TEV-50717 must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator (or designee) will instruct the patient to store TEV-50717 according to the instructions on the label, if applicable; or will give instructions in an appropriate form.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for TEV-50717 accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of IMP accountability (ie, TEV-50717 and other study materials received, used, unused, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused bottles of TEV-50717 that are not destroyed at the site will be returned to the sponsor or designee, as agreed with the sponsor.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

Based on the feedback from the external experts, the optimal dose of tetrabenazine in the treatment of DCP in a pediatric population is individualized and not related to any specific dose per body weight. Also, the 2 published studies (Jain et al 2006, Vuong et al 2004) on the use of tetrabenazine in the treatment of hyperkinetic movement disorders (including DCP) (see Section 1.1.2) introduce a wide range of doses of tetrabenazine that were found to be effective. As variability in optimal dose of tetrabenazine might be due to its highly variable metabolism of the active (α+β)-HTBZ, it is also conceivable that the patients with hyperkinetic movement disorders would require an individually optimized dose. Therefore, this uses a flexible dose design, where maximal dose is limited based on body weight and CYP2D6 impairment status. Based on modeling and simulations of the exposure (area under the plasma concentration-time curve) and maximum observed concentration in adults and adolescents, it is possible to design dosing regimens in alternative body weight categories depending on their CYP2D6 impairment status, which would give comparable exposure and maximum observed concentration across the range of strata. This approach is analogous to what has also been adopted in the ongoing parent Study TV50717-CNS-30080 in DCP and the ongoing TV50717-CNS-30046 Phase 2/3 and TV50717-CNS-30060 Phase 3 studies of TEV-50717 in TS.

5.4. Treatment after the End of the Study

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). The end of study is defined as the date of the week 55 follow-up telephone contact of the last participant.

There are no plans to provide further treatment to patients upon completion of the study. An extension to the study may be considered on an annual basis.

5.5. Restrictions

Medications prohibited before and/or during the study are described in Section 5.6.

While patients receiving a strong CYP2D6 inhibitor (such as paroxetine, fluoxetine, or bupropion) at day 1 may be enrolled into this study, the removal of strong CYP2D6 inhibitors during treatment is discouraged, as this would have an effect on exposure to active circulating drug. If the removal of a strong CYP2D6 inhibitor is required from a clinical perspective, the medical monitor should be contacted so that an appropriate change in TEV-50717 dosage can be made. The addition of a strong CYP inhibitor is prohibited during the study.

Restrictions in regard to sexual activity and required laboratory values are provided in the inclusion and exclusion criteria.

As with other VMAT2 inhibitors (tetrabenazine and reserpine), patients should be advised that the concomitant use of alcohol or other sedating drugs with TEV-50717 may have additive effects and cause or worsen somnolence.

Patients should be advised not to drive a car or operate dangerous machinery until they understand how TEV-50717 affects them.

Use of illicit drugs is prohibited from the time of signing of the ICF and throughout study participation.

Patients may not donate blood from the time of signing of the informed consent, while taking the TEV-50717, and for 14 days after the last dose.

5.6. Prior and Concomitant Medication or Therapy

Any prior or concomitant therapy, medication, or procedure a patient receives during TEV-50717 administration and up to the end of the study period, including follow-up, will be recorded on the CRF Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all medication according to the World Health Organization drug dictionary.

At each clinic visit after screening or day 1 (whichever comes first), the investigator will ask patients and/or caregivers whether the patient has taken any new medications (other than TEV-50717) or has any change in current medications, including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit. Patients and/or caregivers will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered (other than TEV-50717) or there is any change in current medications, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator. Indication, dosage, and start and end dates should be entered on the CRF.

The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP inhibitor. Allowed strong CYP inhibitors at day 1 are shown in Appendix H, Table 11. The addition of a strong CYP inhibitor is prohibited during the study.

Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table 12.

Concomitant medication will be monitored throughout the study.

5.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance until completion of the IMP administration according to the protocol or discontinuation from the IMP. A check of compliance with TEV-50717 intake will be performed during each in-clinic visit and telephone contact and will be documented in each patient's file. TEV-50717 accountability records will be completed during each in-clinic visit.

If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study. Based on pill counts at in-clinic visits, poor compliance with study drug (ie, <80%) or overdose (ie, >105%) is to be recorded as an important deviation and expeditiously reported to the medical monitor.

Patients are expected to participate in this study for its entire duration. Exposure to TEV-50717 will be assessed as required (Section 5.1.1.1).

5.8. Temporary Discontinuation of Investigational Medicinal Product

Refer to Table 5 for data to be collected at the time of TEV-50717 discontinuation and follow-up and for any further evaluations that need to be completed.

If a patient experiences a "clinically significant" adverse event that is attributed to TEV-50717, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible. At the end of the titration period, the patient's initial dose will be established for the maintenance period. The dose of TEV-50717 may be reduced or suspended if a patient experiences an adverse event or tolerability finding during the maintenance period and the investigator believes a dose reduction or suspension is warranted.

Dose adjustments of TEV-50717 (upward or downward) may be made during the maintenance periods, 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 (Table 6 and Table 7). After the dose modification, the patients will remain at the modified dose unless further dose adjustments are warranted, and will otherwise follow the visit schedule as outlined in the protocol.

If a dose reduction occurs before a scheduled clinic visit, the clinic visit will be postponed so that efficacy evaluations can be performed at least 5 days after the change. The reason for a dose reduction must be clearly documented. If the determination that a patient requires a dose modification is made during a telephone contact, an unscheduled clinic visit should be conducted as soon as practicable thereafter.

Suspension of TEV-50717 treatment for up to 1 week, if warranted, is allowed. If a patient's serum potassium or magnesium falls below the lower limit of normal, TEV-50717 should be suspended. Since TEV-50717 does not have any known effect on potassium and magnesium levels, the reference to potassium and magnesium is in the context of other factors related to any current underlying condition, such as severe diarrhea or intake of drugs that lower serum potassium and magnesium. The investigator will be responsible to manage the patient's condition per the site's standard of care and assess continuation of treatment. The medical monitor should be contacted to discuss the suspension and possible resumption of the IMP. TEV-50717 treatment may only be restarted once serum potassium and/or magnesium levels have normalized.

If the patient restarts TEV-50717 within 7 days of suspension, the full dose of TEV-50717 may be resumed without titration at the same dose level or 1 dose lower (last tolerated dose). Suspension of TEV-50717 treatment for adverse events must be reviewed with the medical monitor before TEV-50717 treatment is restarted. Suspensions for more than 7 days must be reviewed by the medical monitor before therapy is restarted, and also to determine if there is adequate time for patients to be reinstated and complete study evaluations. The reason for a dose reduction or suspension must be clearly documented in the related adverse event form.

Dose suspension is allowed during the titration period and the maintenance period. Patients who restart TEV-50717 treatment will remain at the current dose unless further dose adjustments are warranted, and will follow the visit schedule as outlined in the protocol.

If a dose suspension occurs before a scheduled clinic visit, an unscheduled visit should be scheduled as soon as possible. If the determination that a patient requires a dose suspension is made during a telephone contact, an unscheduled clinic visit should be conducted as soon as practicable thereafter.

The patients who restart TEV-50717 treatment will follow the visit schedule as outlined in Table 5. Patients who withdraw from the study will proceed as described in Section 4.3.

5.9. Randomization and Blinding

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

5.10. Maintenance of Randomization and Blinding

5.10.1. Maintenance of Randomization

Not applicable.

5.10.2. Blinding and Unblinding

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

5.10.3. Data Monitoring Committee

There will be an Independent Data Monitoring Committee (IDMC) in this study. Details are given in Appendix B.

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.

The conduct and specific details regarding the IDMC sessions are outlined in the IDMC Charter.

5.11. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 77.5 mL.

Details are provided in Appendix I.

6. ASSESSMENT OF EFFICACY

Efficacy in this study will be evaluated using MD-CRS part I total score, MD-CRS part II total score, CaGI-I, CGI-I, CGI-S, PEDI-CAT, UHDRS-TMS, UHDRS-TMC, UHDRS-TMD, and COPM. 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 all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly. At each study visit, as applicable, the investigator should compare the current scores to the baseline scores.

For COVID-19 updates, refer to Appendix M.

6.1. Assessments of Efficacy

6.1.1. Movement Disorder-Childhood Rating Scale

The MD-CRS was developed as a child-oriented instrument aimed to describe various types of movement disorders (dystonia, chorea, athetosis, ballismus, and hypokinetic-rigid) and to compare changes during natural history and/or pharmacological treatments or to monitor interventions (Battini et al 2008, Battini et al 2014). MD-CRS reliability (eg, inter- and intra-rater reliability) has been evaluated when used by clinicians and professionals of rehabilitation after a 1-day training on its scoring (Sgandurra et al 2018). The version "MD-CRS 4-18" has been designed to evaluate various movement disorders in children and adolescents, aged 4 to 18 years, and their influence on daily living activities or motor function in different body regions at rest and during specific tasks (Battini et al 2008). The MD-CRS has 2 parts: part I for general assessment of the functioning and impact of CP on the activities of the patient and part II for a specific motor assessment of severity of the movement disorder.

The MD-CRS part I evaluates 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) (Battini et al 2008, Battini et al 2014). The minimum score is 0 and the maximum score is 60.

The MD-CRS part II total score is part of the MD-CRS for the age group 4 to 18 years. MD-CRS part II was shown to be suitable for detecting a treatment effect after an intervention with trihexyphenidyl, a drug used to treat dyskinesia in children with CP (Battini et al 2014).

MD-CRS part II evaluates the severity of the movement disorder in a scale of 0 to 4 in 7 body regions, all areas in which dyskinesia can be seen in patients with CP. 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. The 7 body regions are (i) eye and periorbital region, (ii) face, (iii) tongue and perioral region, (iv) neck, (v) trunk, (vi) upper limb, and (vii) lower limb. The MD-CRS part II does not differentiate whether the dyskinesia is of the dystonic or choreiform phenotype, and the worst dyskinesia in any of the regions observed during the assessment session will be taken as the score for each affected body

region. The minimum score is 0 (absent) and the maximum score is 28 (marked/prolonged). Assessment of MD-CRS part II items will be based solely on chorea in this study.

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 (Battini et al 2008). The minimum score is 0 and the maximum score is 1.

The MD-CRS (with video recording) will be administered at the day 1 visit (Table 4) and at week 14, week 27, week 40, week 53/ET, and week 54/follow-up visits (Table 5). The protocol refers to MD-CRS as a physician-rated scale, but in certain instances, based on the experience of the rater, certain non-physicians may be approved to rate the MD-CRS.

Video review of MD-CRS parts I and II for chorea at day 1, week 27, week 53/ET, and week 54/follow-up visits (Table 4 and Table 5) will be assessed in a blinded manner (ie, visit, investigator site rating, and other study related information) by a central review board. Central reading results performed by the central raters will not be disclosed to the investigational site. Central reading details will be provided in a separate charter.

6.1.2. Caregiver Global Impression of Improvement Scale

The CaGI-I is single item questionnaire to assess the caregiver's impression of improvement in dyskinesia symptoms after initiating therapy. The scale is a caregiver-reported outcome that aims to evaluate all aspects of patients' health and determine if there has been an overall improvement or not in dyskinesia symptoms. The CaGI-I is to be completed before all other investigator-rated scales during visits where CaGI-I is collected (Table 5). 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 administered at week 14, week 27, week 40, week 53/ET, and week 54/follow-up visits.

6.1.3. Clinical Global Impression of Improvement Scale

Each time the patient is seen during the treatment period (ie, from day 1 to week 53/ET, at each in-clinic visit or during telephone contacts with non-recording live video), the investigator compares the patient's improvement in overall dyskinesia symptoms to the 1-week period just prior to the day 1 visit (Busner and Targum 2007). The CGI-S score obtained at the day 1 visit (see Section 6.1.4) serves as a good basis for making this assessment. The 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 will be administered at the in-clinic visits (week 3, week 7, week 14, week 27, week 40, week 53/ET, and week 54/follow-up). Patients will also be assessed for CGI-I during telephone contacts (with non-recording live video) at the week 1, week 2, week 4, week 5, week 6, week 21, week 33, and week 46.

6.1.4. Clinical Global Impression of Severity

The investigator uses all available information and total clinical experience with this particular population to assess dyskinesia severity over the past 1-week period prior to the CGI-S assessment on the patient (Busner and Targum 2007). The 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 administered at the day 1 visit (Table 4) and administered at week 14, week 27, week 40, week 53/ET, and week 54/follow-up visits. Input from the caregiver is permitted.

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

The PEDI-CAT is a clinical assessment for children and youth. The PEDI-CAT comprises a comprehensive item bank of 276 functional activities acquired throughout infancy, childhood, and young adulthood. This study will use only the caregiver report. The PEDI-CAT is recommended for use with children approaching 1 year of age and adults up to 21 years of age.

The PEDI-CAT (activities of daily living [ADL], caregiver completed, content-balanced version) 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. This study will use only the content-balanced version of the Daily Activities domain (Dumas and Fragala-Pinkham 2012). 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 (ADL, caregiver completed, content-balanced version) is administered at day 1 and at the week 27 and week 53/ET visits.

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

The UHDRS comprises a broad assessment of features associated with HD. It is a research tool that has been developed to provide a uniform assessment of the clinical features and course of HD. The UHDRS-TMS comprises 15 items and assesses eye movements, speech, alternating hand movements, dystonia, chorea, and gait. The minimum score is 0 (absent) and the maximum score is 108 (worst) (Huntington Study Group 1996).

The UHDRS-TMS is administered at the day 1, week 14, week 27, week 40, and week 53/ET visits.

The 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) (Huntington Study Group 1996).

The 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) (Huntington Study Group 1996).

The UHDRS-TMC (physician rated) score and UHDRS-TMD (physician rated) score will be determined from the UHDRS-TMS assessment. The protocol refers to UHDRS-TMC and UHDRS-TMD as a physician-rated scale, but in certain instances, based on the experience of the rater, certain non-physicians may be approved to rate the UHDRS-TMC and UHDRS-TMD.

A central reading of the UHDRS-TMC and UHDRS-TMD will be performed at baseline/day 1 and at weeks 27, 53/ET, and 54 visits. The central rating will be done for all patients, based on the videos collected for the central rating of MD-CRS. Video review will be assessed periodically in a blinded manner (eg, visit and investigator site rating) by a central review board. Central reading results performed by the central raters will not be disclosed to the investigational site. Central reading details will be provided in a separate charter.

6.1.7. 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, the COPM is a 5-step process which measures individual, patient-identified problem areas in daily function. Two scores, for performance and satisfaction with performance, are obtained (Law et al 1990).

The COPM is administered at day 1 and at the week 27 and week 53/ET visits.

See Table 5 for a detailed description of assessments and procedures.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, vital signs measurements, ECG findings, clinical laboratory test results, physical examination findings (including body weight and height measurements), neurological examination, safety rating scales, medication errors, and use of concomitant medications.

For COVID-19 updates, refer to Appendix M.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to TEV-50717. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions

  (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event.)
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant

  (Note: Abnormal laboratory or diagnostic test results at day 1 that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the follow-up period. The follow-up period of recording of adverse events is defined as 2 weeks after the last dose of TEV-50717.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to TEV-50717. For serious adverse events, the serious adverse event form must be completed, and the serious adverse event must be reported immediately (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to TEV-50717 or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding TEV-50717, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF.

The relationship of each adverse event to TEV-50717 and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Further details are given in the Safety Monitoring Plan.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the following:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product

The relationship of an adverse event to the IMP (ie, TEV-50717) is characterized as follows:

Table 9: The Relationship of an Adverse Event to the IMP

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

IMP=investigational medicinal product.

7.1.5. Serious Adverse Events

For recording of serious adverse events, the study period is defined for each patient as that time period from signature of the ICF to the end of the follow-up period as defined in Section 7.1.2. Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death
- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event that, hypothetically, might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

  Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as all of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3× the upper limit of normal (ULN)
- Tbil increase of >2×ULN
- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is the IB.

A serious adverse event that is not included in the listing of adverse reactions in the RSI by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

The sponsor's Global Patient Safety and Pharmacovigilance (GPSP) personnel will determine the expectedness for all serious adverse events.

For the purpose of suspected unexpected serious adverse reaction (SUSAR) reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of TEV-50717, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (a contract research organization [CRO] in a country without a sponsor LSO, contact information is in the Clinical Study Personnel Contact Information section of this protocol); the LSO will forward the report to the sponsor's GPSP.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of the adverse event
- investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility, reasonable possibility)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness

- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical and psychiatric history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to TEV-50717, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/CRO for submission to the competent authorities, Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), and investigators, according to regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the TEV-50717 or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TEV-50717 and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TEV-50717

7.1.6. Protocol-Defined Adverse Events of Special Interest

No protocol-defined adverse events of special interest for expedited reporting were identified for this study. Events of drug-induced parkinsonism, changes in behavior, and sleepiness will be monitored using standardized scores and presented as part of safety analysis (see Section 7.2).

7.1.7. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study (Section 4.3).

7.2. Safety Rating Scales

Site-administered safety scales include the children's C-SSRS (Posner et al 2011), CBCL, ESRS (Chouinard and Margolese 2005), and ESS (Janssen et al 2017). 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 all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly. At each study visit, as applicable, the investigator should compare the current scores to the baseline scores.

For COVID-19 updates, refer to Appendix M.

7.2.1. Children's Columbia-Suicide Severity Rating Scale

The children's C-SSRS assesses suicidal ideation and behaviors for all patients aged ≥12 years to determine suicide risk.

The children's C-SSRS Since Last Visit is administered at screening and/or day 1, as applicable (Table 4), and at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up (Table 5). However, 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.

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 is an interview by trained study personnel.

The frequency and severity of suicidal ideation or behavior according to the children's C-SSRS questionnaire will be presented by visit and by treatment group. A shift table for children's C-SSRS categories at day 1, compared to the worst (highest) category during the treatment period, will be presented.

7.2.2. Extrapyramidal Symptom Rating Scale

The ESRS was designed to assess 4 types of drug-induced movement disorders: parkinsonism, akathisia, dystonia, and TD (Chouinard and Margolese 2005). In this study, parkinsonism and

akathisia will be evaluated with subscales I (subjective questionnaire) and II (evaluation for parkinsonism/akathisia). The ESRS is administered at the day 1 visit (Table 4) and administered at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits (Table 5).

Subscale I of the ESRS questionnaire rates subjective parkinsonism/akathisia at periods other than the day of examinations during the last 7 days. It is scored on a 4-point scale (0=Absent, 1=Mild, 2=Moderate, or 3=Severe). The evaluation takes into account the verbal report of the patient on the following: 1) the frequency and duration of the symptom during the day, 2) the number of days the symptom was present during the last week, and 3) the subjective evaluation of the intensity of the symptom by the patient.

Subscale II of the ESRS questionnaire for evaluation of parkinsonism and akathisia includes 17 items with scores ranging from 0 to 102 to assess the following: tremor (0 to 48), gait and posture (0 to 6), postural stability (0 to 6), rigidity (0 to 24), expressive automatic movements (0 to 6), bradykinesia (0 to 6), and akathisia (0 to 6).

7.2.3. Child Behavior Checklist (for Ages 6 to 18)

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

The Competence Scale (Parts I to VII) assesses various activities (eg, sports, hobbies, games, organizations, clubs, teams, groups, jobs, and chores), interpersonal relationships, and academic performance.

The Syndrome Scale comprises 118 questions related to problem behaviors. This study will use a recall period of "now or within the last week," representing a modification from the original scale, which was "now or within the last 6 months". For each item, the 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 CBCL is part of the Achenbach System of Empirically Based Assessment that identifies syndromes that are behavioral clusters that indicate certain types of behavioral, social, or emotional problems (Achenbach and Rescorla 2004). The problem behaviors are scored on the following 8 empirically based syndromes: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior.

The Competence and Syndrome Scales are displayed on profiles in relation to gender and age-specific percentiles and T scores based on national normative samples.

The full CBCL assessment (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) will be completed at the screening or day 1 visit, as applicable (Table 4) and at the week 53/ET visit (Table 5). The Syndrome Scale part of the CBCL [behavioral items] will be completed at day 1, as applicable (Table 4) and at weeks 3, 7, 14, 27, 40, and 54/follow-up visits (Table 5).

7.2.4. Epworth Sleepiness Scale (for Children and Adolescents)

The 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). Johns (2015) proposed the ESS as the official modified version of the ESS for children and adolescents. Janssen et al (2017) published results of their validation analysis and concluded that the ESS developed for children and adolescents is a reliable and internally valid measure of daytime sleepiness in adolescents 12 to 18 years of age, but further studies are needed to establish the internal validity of the questionnaire for children under 12 years and the external validity and accuracy of cut-off points for children and adolescents.

The ESS is administered at the screening and/or day 1 visit, as applicable (Table 4) and administered at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits (Table 5). For patients 6 to 12 years of age, the ESS will be completed by the caregiver. For patients ≥13 years of age, the ESS will be completed by the patient. Input from the caregiver is permitted.

The ESS asks respondents to rate, on a 4-point Likert scale (0 to 3), their usual chances of dozing off or falling asleep in different situations or activities that most people engage in as part of their daily lives. The total ESS score is the sum of 8 item scores and can range between 0 and 24, with the higher the score indicating a higher level of daytime sleepiness. Most people can complete the ESS without assistance in 2 or 3 minutes.

Categories

- 0=would never fall asleep
- 1=slight chance of falling asleep
- 2=moderate chance of falling asleep
- 3=high chance of falling asleep

7.3. Pregnancy

Any female patient becoming pregnant during the study will discontinue TEV-50717.

All pregnancies of female patients participating in the study that occur since the week 15 visit of Study TV50717-CNS-30080, during Study TV50717-CNS-30081, or within 14 days after the end of study are to be reported immediately once the investigator has become aware of the pregnancy. The pregnancy should be reported to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3).

All female patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy in the female patient participating in the study does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event and also complete the pregnancy form.
- For an elective abortion due to developmental anomalies, report as a serious adverse event and also complete the pregnancy form.
- For an elective abortion **not** due to developmental anomalies, complete the pregnancy form; do not report as an adverse event.

7.4. Medication Error and Special Situations Related to the Investigational Medicinal Product

Any administration of IMP that is not in accordance with the study protocol should be reported on the CRF as a deviation in the patient's source documents, regardless of whether or not an adverse event occurs as a result, if it meets the deviation criteria specified in the protocol (Appendix D).

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (ie, TEV-50717), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP, which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.
7. Breastfeeding: Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk.

7.5. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant

- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic work-up. (Note: Abnormal laboratory or diagnostic test results at day 1 that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

For COVID-19 updates, refer to Appendix M.

Table 10: Clinical Laboratory Tests

Serum Chemistry	Hematology and Coagulation	Urinalysis
Calcium	Hemoglobin	Protein
Phosphate	Hematocrit	Glucose
Sodium	Erythrocytes	Ketones
Potassium	Platelets	Hemoglobin
Chloride	Leucocytes	pH
Creatinine	– Neutrophils	Specific gravity
Glucose	– Lymphocytes	Microscopic tests
Magnesium	– Eosinophils	– Bacteria
Blood urea nitrogen	– Monocytes	– Erythrocytes
Total cholesterol	– Basophils	– Leucocytes
Triglycerides	Lymphocytes atypical	– Crystals
Uric acid	– Prothrombin International Normalized Ratio (INR)	– Casts
Alanine aminotransferase		
Aspartate aminotransferase		
Lactate dehydrogenase		
Alkaline phosphatase		
Bicarbonate or carbon dioxide		
Protein		
Albumin		
Bilirubin		
Direct bilirubin		

7.5.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis) will be performed at the time points detailed in Table 4 and Table 5 (ie, screening and weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided in Table 10.

7.5.2. Other Clinical Laboratory Tests

7.5.2.1. Beta-Human Chorionic Gonadotropin Tests

For females who are postmenarchal or ≥12 years of age, the following β-HCG tests in urine or serum will be performed based on when the patient enrolls in the study:

- If the patient enrolls between 1 and <2 weeks after the week 15 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, 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.
- If the patient enrolls between 2 and ≤4 weeks after the week 15 visit of Study TV50717-CNS-30080 and does not have a clinically significant change, β-HCG tests in urine will be administered at day 1.
- If the patient enrolls between 2 and ≤4 weeks after the week 15 visit of Study TV50717-CNS-30080 and has a clinically significant change, β-HCG tests in serum will be administered at screening. A β-HCG test in urine will be performed at the day 1 visit.

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.

During the treatment period, β-HCG tests in urine will be performed for females who are postmenarchal or ≥12 years of age at weeks 14, 27, 40, and 54/follow-up. β-HCG tests in serum will be performed for all female patients who are postmenarchal or ≥12 years of age at week 53/ET and if clinically indicated.

7.5.2.2. Urine Drug Screen

A urine drug screen will be performed at the time points specified in Table 4 and Table 5. The urine drug screen detects the presence of drugs of abuse. Additionally, the urine drug screen will detect the presence of drugs prohibited according to the laboratory manual. If a given parameter cannot be tested using urine, an alternative matrix (eg, serum) may be considered acceptable. The sponsor's medical expert must be made aware in advance of, and provide approval for, drug screen parameters to which this will apply.

A positive result for any drugs of abuse or their metabolites or drugs prohibited according to the laboratory manual, without medical explanation, will preclude the patient from enrollment or continued participation in the study. Some of the drugs or drug classes listed in this urine drug screen may be permitted in certain cases when the particular medication is being used under a physician's or clinician's guidance and in compliance with the physician's/clinician's recommendation for a specific condition; for example, barbiturates for seizures, amphetamines for attention deficit hyperactivity disorder, and opiates or oxycodone for pain, if the dosing has been stable for at least 4 weeks before screening or day 1 and if no changes to dose or frequency are anticipated during the course of the study. Such cases should be discussed with the medical monitor. For patients who are either using these medications or who have a positive drug screen

for these substances or derivatives, such cases should be submitted to the medical monitor for consideration of participation in this study. If per the investigator's judgment, however, a patient does not meet the criteria for substance use disorder, a positive drug screen for these medications or derivatives, without medical explanation, should be discussed on a case-by-case basis with the medical monitor to determine the patient's eligibility, based on the information available.

7.6. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, body temperature, and pulse) will be measured at the time points detailed in Table 4 and Table 5. All abnormal vital signs will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Before blood pressure and pulse are measured, the patient must rest in a supine or semi-erect/seated position 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 blood pressure 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).

For any abnormal vital sign value, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event and monitored as described in Section 7.1.2.

For COVID-19 updates, refer to Appendix M.

7.7. Physical Examination

Physical examinations, including height and weight, general appearance, skin, head, eyes, ears, nose, throat, neck, lymph nodes, cardiovascular, respiratory, musculoskeletal, abdominal, and extremities, will be performed at the time points detailed in Table 4 and Table 5.

Weight must be measured with shoes and outerwear off.

Any new physical examination finding (ie, since day 1) that is judged by the investigator as clinically significant will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

Investigators should pay special attention to clinical signs related to previous serious diseases.

7.8. Neurological Examinations

Neurological examination, including mental status, cranial nerves, motor system (strength, tone, and posture), coordination, gait and balance, tendon reflexes, and sensation, will be performed at the time points detailed in Table 4 and Table 5. Any neurological examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with the day 1 value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.9. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 4 and Table 5. All ECGs will be performed after at least 5-minute rest in a supine or semi-supine position. The investigator should review the ECG at day 1 and at screening (in case a screening visit is performed) to determine patient eligibility for the study and subsequent ECGs for the patient's continuation in the study. A qualified physician at a central diagnostic center will be interpreting the ECG.

The ECG types are defined as follows:

- A "standard ECG" is a "standard" 10-second 12-lead ECG.
- A "summary ECG" is a continuously recorded ECG of longer than 10 seconds. For a "summary ECG," the minimal recommended duration is 2 minutes or longer, and the preferred duration is 5 minutes (as it provides the most robust result). If a "summary ECG" is less than 2 minutes, data will still be captured and analyzed to the extent possible.

The investigator should review the ECG at screening to determine patient eligibility for the study and subsequent ECGs for the patient's continuation in the study. All ECGs should be reviewed by the investigator for any clinically significant findings during the visit, and before the patient leaves the clinic. A qualified physician at Spaulding (the central diagnostic center) will interpret the ECG.

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

Any ECG finding that is judged by the investigator as clinically significant will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2.

The criteria for an abnormal post-baseline QTcF are a value >500 msec or change from screening >60 msec. If one of these criteria is met, the investigator must further evaluate the QTcF as follows:

- If a standard ECG is abnormal and meets the above protocol criteria:
  - A 5-minute summary ECG recording should be performed at the research site, and a repeat standard ECG is not required. The site should follow the process to have these ECGs read by Spaulding.
  - If a 5-minute summary ECG cannot be performed (for instance, if the patient is evaluated at a facility other than the research site, and the summary ECG is not available), the investigator should obtain 2 repeat standard ECGs and determine the average of these 3 post-screening QTcF values. The site should follow the process to have these ECGs read by Spaulding.

- The investigator should then compare the post-screening QTcF values to the pre-treatment QTcF values at screening. As noted above, the post-screening QTcF values will use either the average QTcF from the 3 post-screening standard ECGs or the QTcF from the summary ECG. The IMP must be stopped for any confirmed post-baseline QTcF average value >500 msec or average increase from screening >60 msec.

For COVID-19 updates, refer to Appendix M.

7.10. Assessment of Suicidality

TEV-50717 is considered to be central nervous system-active. In addition, there have been some reports of suicidal ideation or behavior as reported in the product label when it has been given to some patients with certain conditions. The sponsor considers it important to monitor for such events before and during this clinical study.

Some central nervous system-active IMPs may be associated with an increased risk of suicidal ideation or behavior when given to some patients with certain conditions. Although this IMP or other similar medicinal products in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to this study population, the sponsor considers it important to monitor for such events before or during this clinical study.

The study population being administered with TEV-50717 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing TEV-50717 in patients who experience signs of suicidal ideation or behavior.

Caregivers of patients being treated with TEV-50717 should be instructed to monitor patients for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Day 1 assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed during the study using the children's C-SSRS described in Section 7.2.

Patients with a positive children's C-SSRS suicidal ideation score on either items 1 or 2 must be 1) discussed with the study medical monitor, 2) re-evaluated within 2 to 3 days in a clinic visit, and 3) treated according to the investigator's medical judgment. Consultation with a child/adolescent psychiatrist or licensed child/adolescent mental health provider is advised, followed by close ongoing monitoring.

If patients endorse or report a children's C-SSRS suicidal ideation score of 3, 4, or 5, the patients will be evaluated immediately by the investigator and referred for psychiatric evaluation. The medical monitor will be immediately consulted. If it is determined by the investigator, the medical monitor, and consulting psychiatrist that exposure to the IMP may have contributed to a change in children's C-SSRS and/or increased depressive symptoms, study medication will be immediately discontinued and the patient will be terminated from the study. In cases where it is determined that IMP did not contribute to changes in depression or suicidality, the investigator will consult with the medical monitor, consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.

If patients report any suicidal behavior that is an actual attempt as assessed in the children's C-SSRS, they will be evaluated immediately by the investigator, referred for psychiatric evaluation, and terminated from the study.

If patients report any suicidal behavior that is interrupted, aborted, or preparatory as assessed in the children's C-SSRS, they will be evaluated immediately by the investigator and referred for psychiatric evaluation. In cases where it is determined in the psychiatric evaluation that IMP did not contribute to changes in suicidal behavior, the investigator will consult with the medical monitor, consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.

7.11. Assessment of Depression

Caregivers of patients are instructed to monitor the patients for any changes in or new onset of depressive symptoms and unusual changes in mood, cognition, or behavior, and to report such symptoms immediately to the investigator. Telephone contacts (with non-recording live video) and clinic visits also allow opportunities for the investigator to assess adverse events.

If a relevant change in status is identified, patients will be seen immediately for an unscheduled visit by the investigator and discussed with the medical monitor. The patient will be referred for further psychiatric evaluation if there is any suspicion of experiencing depression. The investigator will record these symptoms as an adverse event of depression. If it is determined by the investigator, after consultation with the medical monitor and consulting psychiatrist, that exposure to the IMP may have contributed to the adverse event of depression, the study medication will be immediately discontinued and the patient will be terminated from the study. Follow-up with a pediatric psychiatrist or licensed child/adolescent mental health provider will be arranged.

In cases where it is determined that IMP did not contribute to the adverse event of depression, the investigator will consult with the medical monitor and/or sponsor to determine whether the patient should continue in the study.

7.12. Concomitant Medication or Treatment

Concomitant therapy or medication usage will be monitored throughout the study according to time points detailed in Table 4 and Table 5. Patients and/or caregivers will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered (other than TEV-50717) or there is any change in current medications, including over-the-counter medications. Any prescribed/administered medication should be reviewed with the investigator.

Patients may be included in this study if they are using cannabis or formulations or derivatives of cannabis in relatively stable amounts, for medical purposes (where applicable according to local regulation), under the guidance, supervision, or prescription of a clinician and anticipated to remain stable (dose and frequency) within the study duration. Patients who are either using cannabis or its derivatives or formulations or patients who have a positive drug screen for cannabis or its derivatives or formulations must be submitted to the medical monitor for consideration of participation in this study. If per the investigator's judgment, however, a patient does not meet the criteria for substance use disorder, a positive drug screen for cannabis or its

metabolites, without medical explanation, will be discussed on a case-by-case basis between the research site, the Medical Monitor, and the sponsor to determine the patient's eligibility, based on the information available. Patients should be advised that the recreational use of cannabis or its derivatives or formulations should be avoided during this study.

Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix H, Table 11. Certain considerations mentioned in the table require the review of the medical monitor. Changes to the allowed medications may be permitted in the context of this study if pre-approved by the medical monitor.

The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP2D6 inhibitor. Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table 12.

7.13. Methods and Time Points of Assessing, Recording, and Analyzing Safety Data

All adverse events will be reviewed on a periodic basis by the clinical project physician/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for TEV-50717) as preliminary safety databases become available.

Methods and time points of assessing safety data are discussed in Section 3.5. Procedures for recording safety data are discussed in Appendix K, and methods of analyses are discussed in Section 9.6.

8. ASSESSMENT OF PHARMACOKINETICS/PHARMACODYNAMICS AND PHARMACOGENETICS

8.1. Pharmacokinetic Assessment

Pharmacokinetic parameters are not evaluated in this study.

8.2. Pharmacodynamics Assessment

Pharmacodynamic parameters are not evaluated in this study.

8.3. Assessment of Exploratory Biomarkers

Biomarkers are not evaluated in this study.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the Statistical Analysis Plan. After finalization of the Statistical Analysis Plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report (CSR).

For COVID-19 updates, refer to Appendix M.

9.1. 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.

9.2. Analysis Sets

A single analysis set is defined for this clinical study, the intent-to-treat (ITT) analysis set.

9.2.1. Intent-to-Treat Analysis Set

The 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 reported in the database. All analyses will be based on the ITT analysis set.

9.2.2. Additional Analyses Sets

Additional analysis sets may be defined in the Statistical Analysis Plan.

9.3. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses.

9.4. Study Population

The ITT analysis set (Section 9.2) will be used for all study population summaries unless otherwise specified. Summaries will be presented for all patients.

9.4.1. Patient Disposition

Data from patients who are enrolled, patients enrolled but not treated (and the reason), patients in the ITT analysis set, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics (day 1), including medical and psychiatric history, prior medications and therapies, and ECG findings, will be summarized using descriptive statistics and will be analyzed by age group. For continuous variables, descriptive statistics will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.5. Multiple Comparisons and Multiplicity

This does not apply to this study.

9.6. Safety Endpoints and Analysis

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 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

Safety analyses will be presented for the ITT analysis set (Section 9.2.1). Patients who did not receive any TEV-50717 will be excluded from the summaries and presented in listings only.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to TEV-50717 (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Observed values and changes from day 1 in laboratory results and vital signs will be summarized descriptively.

Observed values in ECG parameters will be summarized, and counts and percentages of abnormal findings will be presented. Changes from baseline of the parent study in ECG parameters will be summarized descriptively. In addition, the number and percentage of patients with on-treatment QTcF values >450, >480, or >500 msec and change from day 1 >30 or >60 msec will be presented.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with TEV-50717.

The frequency and severity of suicidal ideation or behavior according to the children's C-SSRS questionnaire will be presented by visit. A shift table for children's C-SSRS categories at day 1, compared to the worst (highest) category during the treatment period, will be presented.

Assessment of drug-induced parkinsonism according to the ESRS (subscales I and II), assessment of change in behavior according to the CBCL questionnaire, and assessment of sedation according to the ESS questionnaire will be summarized descriptively.

Safety assessments and time points are provided in Table 5.

For continuous variables, descriptive statistics will be provided for actual values and changes from day 1 to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well.

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.

9.7. Efficacy Analysis

No formal inferential statistics will be applied to the efficacy endpoints.

Efficacy Endpoints

The following efficacy endpoints will be assessed in this study:

- 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 (activities of daily living, caregiver completed, content-balanced version)
- UHDRS-TMC (centrally read)
- UHDRS-TMD (centrally read)
- UHDRS-TMS (physician rated)
- UHDRS-TMC (physician rated)
- UHDRS-TMD (physician rated)

- COPM (physician rated)

Planned Method of Analysis

The ITT analysis set (see Section 9.2.1) will be used for all efficacy analyses. Summaries will be presented for all patients. Descriptive statistics will be used to summarize efficacy measures. Descriptive statistics of change-from-day 1 will utilize day 1 from the present open-label study (Study TEV-50717-30081).

Patients who did not receive any TEV-50717 will be excluded from the summaries and presented in listings only. For continuous variables, descriptive statistics will be provided for actual values and changes from day 1 to each time point. For categorical variables, patient counts and percentages will be provided.

9.8. Tolerability Analysis

Tolerability was not specifically defined.

9.9. Planned Interim Analysis

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.

9.10. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the statistical analysis plan, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix D for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

Refer to Appendix J for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

For COVID-19 updates, refer to Appendix M.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for GCP E6, and any applicable national and local laws and regulations (eg, Title 21 CFR [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with competent authorities.

See Appendix E for the ethics expectations of informed consent or assent, competent authorities and IEC and IRC, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix K for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

13. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the IMP is delivered.

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are, for example, damages to health and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete Food and Drug Administration 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. PUBLICATION POLICY

See Appendix L for information regarding the publication policy.

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 04 Dated 01 June 2022

The primary reason for this amendment is to adjust the sample size and to add new endpoints.

All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typographical errors, punctuation, etc) have been made to the protocol and protocol synopsis, as appropriate.

Table 4 (Study Procedures and Assessments - Screening and/or Day 1), Table 5 (Study Procedures and Assessments: Titration, Maintenance, and Follow-up Periods), and Figure 1 (Overall Study Schematic Diagram) have been revised to reflect changes described below.

Protocol text with changes shown	New wording	Reason/justification for change
1. INTRODUCTION		
Botulinum neurotoxin A is also in clinical use for the treatment of spasticity and dystonia and is considered modestly effective in selected patients, but it does not meet the full treatment need. ~~Naxibimols, a non-smoked cannabis derivative, was approved to treat spasticity associated with multiple sclerosis in the United Kingdom in 2010 and is being investigated to treat spasticity in CP (ClinicalTrials.gov Identifier: NCT01898520).~~ Currently, there are very few agents with novel mechanisms of action in development for movement disorders in CP. ~~Dalfampridine, a small-molecule potassium channel blocker thought to restore conduction in central demyelinated axons, is approved for use in multiple sclerosis but has failed to demonstrate functional improvement in patients with CP (Bethoux et al 2017).~~	Botulinum neurotoxin A is also in clinical use for the treatment of spasticity and dystonia and is considered modestly effective in selected patients, but it does not meet the full treatment need. Currently, there are very few agents with novel mechanisms of action in development for movement disorders in CP.	New information indicates Naxibimols and Dalfampridine will not be used for DCP and therefore not relevant to this protocol.
1.2.2. Clinical Studies		
The clinical development plan for TEV-50717 to date includes the following: • fourteen~~Thirteen~~ completed Phase 1 studies in healthy adult volunteers • two completed pivotal Phase 2/3 and Phase 3 studies in patients with TD • one ~~ongoing~~completed Phase 3 long-term safety study in patients with TD • two completed pivotal studies in patients with TS • one terminated Phase 3 long-term safety study in patients with TS	The clinical development plan for TEV-50717 to date includes the following: • fourteen completed Phase 1 studies in healthy adult volunteers • two completed pivotal Phase 2/3 and Phase 3 studies in patients with TD • one completed Phase 3 long-term safety study in patients with TD • two completed pivotal studies in patients with TS • one terminated Phase 3 long-term safety study in patients with TS	Updated the status of the TEV-50717 studies that have been conducted/completed since the last amendment.
1.2.2.1. Clinical Pharmacology Studies		
Fourteen~~Thirteen~~ Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers.	Fourteen Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers.	Updated the status of the TEV-50717 studies that have been conducted/completed since the last amendment.

Protocol text with changes shown	New wording	Reason/justification for change
1.2.2.2. Clinical Safety and Efficacy Studies		
The safety profile of TEV-50717 has been characterized to date in healthy volunteers, as well as in adult patients with chorea associated with HD and TD (as detailed in the IB) and in children and adolescents with TS.	The safety profile of TEV-50717 has been characterized to date in healthy volunteers, as well as in adult patients with chorea associated with HD and TD (as detailed in the IB) and in children and adolescents with TS.	Text updated to include the TS studies as part of the safety profile for TEV-50717
See new wording column	Studies TV50717-CNS-30046 and TV50717-CNS-30060 evaluated children and adolescent patients with tics associated with TS. Neither study met the primary efficacy endpoint. In both studies, TEV-50717 was generally safe and well tolerated. No deaths occurred in either study. One patient had 2 serious adverse events. There were no trends in changes from baseline in serum laboratory, vital signs, ECG, and physical and neurological parameters. There was no evidence of a new safety signal in pediatric patients with TS treated with TEV-50717 in comparison to the known safety profile of this drug in adult patients with HD or TD. The open-label, long-term Study TV50717-CNS-30047 evaluated children and adolescent patients with tics associated with TS. Treatment with TEV-50717 through 54 weeks resulted in improvement of tics. The safety profile observed in pediatric patients with TS receiving long-term treatment with TEV-50717 was generally comparable to the known safety profile of this drug in adult patients with HD or TD, with the exception of the adverse event of weight gain.	Text added for the recently completed TS studies
1.3.1.2. Potential Risks of TEV-50717		
The following information is based on clinical trial experience with TEV-50717 and the US prescribing information for Xenazine (tetrabenazine) and Austedo (deutetrabenazine):	The following information is based on clinical trial experience with TEV-50717 and the US prescribing information for Xenazine (tetrabenazine) and Austedo (deutetrabenazine):	Clarification
See new wording column	• TEV-50717 is contraindicated in patients taking tetrabenazine or valbenazine. At least 30 days should elapse after stopping tetrabenazine or valbenazine before starting TEV-50717.	Updated per the current prescribing info of Austedo

Protocol text with changes shown	New wording	Reason/justification for change
2.1. Primary and Secondary Study Objectives and Endpoints		
See new wording column	• MD-CRS part I total score (centrally read) • MD-CRS part II total score (centrally read) • UHDRS-TMC (centrally read) • UHDRS-TMD (centrally read)	New secondary endpoints
3.1. General Study Design and Study Schematic Diagram		
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 ~~6 months~~4 weeks following the week 15 visit of the TV50717-CNS-30080 study.	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 the TV50717-CNS-30080 study.	Change to the time period patients can enroll following end of Study 30080 due to changing situation of the COVID-19 pandemic
Patients can either enroll in the study at the week 16 visit of Study TV50717-CNS-30080 or up to ~~6 months~~4 weeks following the week 15 visit of Study TV50717-CNS-30080.	Patients can either enroll in the study at the week 16 visit of Study TV50717-CNS-30080 or up to 4 weeks following the week 15 visit of Study TV50717-CNS-30080.	Change to the time period patients can enroll following end of Study 30080 due to changing situation of the COVID-19 pandemic
The following text was deleted: Day 1: More than 4 weeks and up to 6 months after Study TV50717-CNS-30080 week 15 visit: The patient will undergo all screening procedures outlined in Table 4. 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. For patients who enroll in the study more than 4 weeks and up to 6 months after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.		Change to the time period patients can enroll following end of Study 30080 due to changing situation of the COVID-19 pandemic

Protocol text with changes shown	New wording	Reason/justification for change
Patients will receive 6 mg of TEV-50717 ~~on the morning of day 2~~ (Table 6). 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.	Patients will receive 6 mg of TEV-50717 (Table 6). 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.	Text revised for consistency with other sections of protocol
Figure 2: Flow Chart for Patient Screening and Day 1 Visit Assessments		
See new wording column	Figure 2 has been revised to remove the Day 1 option for enrollment >4 weeks for consistency with the rest of the changes to the protocol	Change to the time period patients can enroll following end of Study 30080 due to changing situation of the COVID-19 pandemic
3.2. Planned Number of Patients and Regions		
~~Up to a~~Approximately ~~185~~45 patients ~~(up to a maximum of 230 patients)~~ who have completed parent Study TV50717-CNS-30080 are planned for enrollment into this study. This study is planned to be conducted in approximately ~~70~~35 investigational centers in North America, ~~and the~~ Europe, and Africa~~an Union~~. ~~The study is expected to start by the end of Q1 2020 and last until Q2 2023.~~	Approximately 45 patients who have completed parent Study TV50717-CNS-30080 are planned for enrollment into this study. This study is planned to be conducted in approximately 35 investigational centers in North America, Europe, and Africa.	Text revised to account for the change in sample size and the removal of the second interim analysis
Table 4: Study Procedures and Assessments: Screening and/or Day 1		
See new wording column	Table 4 has been revised as described below: • Remove the Day 1 option for enrollment >4 weeks for consistency with the rest of the changes to the protocol • Add new secondary endpoints: MD-CRS parts I and II (centrally read), UHDRS-TMC (centrally read), and UHDRS-TMD (centrally read)	Revised to clarify and align the schedule of events and its corresponding footnotes against the updates included throughout the study design and body of the protocol

Protocol text with changes shown	New wording	Reason/justification for change
Table 5: Study Procedures and Assessments: Titration, Maintenance, and Follow-up Periods		
See new wording column	Table 4 has been revised as described below: • Add new secondary endpoints: MD-CRS parts I and II (centrally read), UHDRS-TMC (centrally read), and UHDRS-TMD (centrally read)	Revised to clarify and align the schedule of events and its corresponding footnotes against the updates included throughout the study design and body of the protocol
4.1. Patient Inclusion Criteria		
f. In the investigator's opinion, the patient and/or caregiver ~~have~~has the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed.	f. In the investigator's opinion, the patient and/or caregiver has the ability to understand the nature of the study and its procedures, and the patient is expected to complete the study as designed.	Revised to clarify the caregiver's role in understanding the nature of the study.
4.3. Withdrawal Criteria and Procedures for the Patient		
See new wording column	If a patient who experiences signs of suicidal ideation or behavior (Section 7.10), the investigator should consult with the medical monitor to determine whether the patient should continue in the study. If a patient reports any suicidal behavior that is an actual attempt as assessed in the children's C SSRS, the patient will be evaluated immediately by the investigator, referred for psychiatric evaluation, and terminated from the study.	Added to align with Section 7.10
Patients experiencing an adverse event leading to discontinuation of TEV-50717~~,~~ or experiencing any other adverse event ~~at the discretion of the investigator~~, should have a single blood sample collected ~~as soon as possible after the adverse event and within 48 hours~~ 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.	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- 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.	

Protocol text with changes shown	New wording	Reason/justification for change
5.1.1.2. Dose Modification and Dose Stratification		
See new wording column	All IMP adjustments are made only after a remote or in-clinic visit; if the dose is escalated, the dose escalation will occur with the next morning's dose.	Revised to match similar change in Administrative Letter #07
• Dose increases may not occur more frequently than every 5 days, except for patients ≥40 kg/88 lbs. For patients ≥40 kg/88 lbs, the first dose increase ~~may~~should be performed in an interval less than 5 days, only once, on day 3.	• Dose increases may not occur more frequently than every 5 days, except for patients ≥40 kg/88 lbs. For patients ≥40 kg/88 lbs, the first dose increase should be performed in an interval less than 5 days, only once, on day 3.	Revised for clarity
• At an in-clinic visit, a ~~A~~dose reduction, if required, should be made to the previously tolerated dose level. **If more than 1 dose reduction is required for an adverse event, the medical monitor should be notified.**	• At an in-clinic visit, a dose reduction, if required, should be made to the previously tolerated dose level. **If more than 1 dose reduction is required for an adverse event, the medical monitor should be notified.**	Revised for clarity
• During the titration period, the dose of IMP should be adjusted according to Table 6 to identify a dose level that optimally reduces dyskinesia (as determined by the investigator, as indicated by a reduction in the CGI-I) and is well tolerated. Dose adjustments should ONLY take place after a telephone or in-clinic visit.	• During the titration period, the dose of IMP should be adjusted according to Table 6 to identify a dose level that optimally reduces dyskinesia (as determined by the investigator, as indicated by a reduction in the CGI-I) and is well tolerated. Dose adjustments should ONLY take place after a telephone or in-clinic visit.	Revised for clarity
Table 6: Maximum Daily Dose of IMP During the Titration Period by Week and Weight Category at Baseline		
See new wording column	Table 6 has been revised as described below: • The title was changed from "by Study Day" to "by Week". • Study day column was changed from "Study day" to "Study time period", and the time periods were changed to weeks. • The footnotes were revised to make consistent with the changes to the table and the body of the protocol.	Revised for clarity

Protocol text with changes shown	New wording	Reason/justification for change
Table 8: Investigational Medicinal Products Used in the Study		
See new wording column	The footnote to Table 8 has been revised as described below: • Reference to the specific section of the pharmacy manual has been removed	Revised for clarity
5.2.1. Storage and Security		
For additional information related to IMP storage conditions, please refer to ~~Section 10 of~~ the Pharmacy Manual.	For additional information related to IMP storage conditions, please refer to the Pharmacy Manual.	Revised for clarity
A record of IMP accountability (ie, TEV-50717 and other study materials received, used, unused, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused bottles of TEV-50717 that are not destroyed at the site will be returned to the sponsor or designee, as agreed with the sponsor.	A record of IMP accountability (ie, TEV-50717 and other study materials received, used, unused, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused bottles of TEV-50717 that are not destroyed at the site will be returned to the sponsor or designee, as agreed with the sponsor.	Revised for clarity
5.7. Procedures for Monitoring Patient Compliance		
The investigator will be responsible for monitoring patient compliance until completion of the IMP administration according to the protocol or discontinuation from the IMP.	The investigator will be responsible for monitoring patient compliance until completion of the IMP administration according to the protocol or discontinuation from the IMP.	Revised for clarity
Based on pill counts at in-clinic visits, poor compliance with study drug (ie, <80%) or overdose (ie, >105%) is to be recorded as an important deviation and expeditiously reported to the medical monitor.	Based on pill counts at in-clinic visits, poor compliance with study drug (ie, <80%) or overdose (ie, >105%) is to be recorded as an important deviation and expeditiously reported to the medical monitor.	Revised for clarity

Protocol text with changes shown	New wording	Reason/justification for change
6.1.1. Movement Disorder-Childhood Rating Scale		
See new wording column	Video review of MD-CRS for chorea at day 1, week 27, week 53/ET, and week 54/follow-up visits (Table 5) will be assessed in a blinded manner (ie, visit, investigator site rating, and other study related information) by a central review board. Central reading results performed by the central raters will not be disclosed to the investigational site. Central reading details will be provided in a separate charter.	Text added to account for the addition of the new endpoint
6.1.3. Clinical Global Impression of Improvement Scale		
Patients will also be assessed for CGI-I during telephone contacts (with non-recording live video) at the week 1, week 2, week 4, week 5, week 6, week 21, week 33, and week 46~~, and week 55/follow-up visits~~.	Patients will also be assessed for CGI-I during telephone contacts (with non-recording live video) at the week 1, week 2, week 4, week 5, week 6, week 21, week 33, and week 46.	The endpoint will not be assed at the follow-up visits.
6.1.6. Unified Huntington's Disease Rating Scale-Total Motor Score		
See new wording column	The UHDRS-TMC (physician rated) score and UHDRS-TMD (physician rated) score will be determined from the UHDRS-TMS assessment. The protocol refers to UHDRS-TMC and UHDRS-TMD as a physician-rated scale, but in certain instances, based on the experience of the rater, certain non-physicians may be approved to rate the UHDRS-TMC and UHDRS-TMD. A central reading of the UHDRS-TMC will be performed at baseline/day 1 and at weeks 27, 53/ET, and 54 visits. The central rating will be done for all patients, based on the videos collected for the central rating of MD-CRS. Video review will be assessed periodically in a blinded manner (eg, visit and investigator site rating) by a central review board. Central reading results performed by the central raters will not be disclosed to the investigational site. Central reading details will be provided in a separate charter.	Text added to account for the addition of the new endpoints

Protocol text with changes shown	New wording	Reason/justification for change
7.2.4. Epworth Sleepiness Scale (for Children and Adolescents)		
See new wording column	For patients 6 to 12 years of age, the ESS will be completed by the caregiver. For patients ≥13 years of age, the ESS will be completed by the patient. Input from the caregiver is permitted.	Clarification
7.5.2.1. Beta-Human Chorionic Gonadotropin Tests		
• If the patient enrolls between 2 and ≤4 weeks after the week 15 visit of Study TV50717-CNS-30080 and has a clinically significant change ~~OR enrolls more than 4 weeks and up to 6 months after the week 15 visit of Study TV50717-CNS-30080~~, β-HCG tests in serum will be administered at screening. A β-HCG test in urine will be performed at the day 1 visit.	• If the patient enrolls between 2 and ≤4 weeks after the week 15 visit of Study TV50717-CNS-30080 and has a clinically significant change, β-HCG tests in serum will be administered at screening. A β-HCG test in urine will be performed at the day 1 visit.	Change to the time period patients can enroll following end of Study 30080 due to changing situation of the COVID-19 pandemic
7.9. Electrocardiography		
See new wording column	The ECG types are defined as follows: • A "standard ECG" is a "standard" 10-second 12-lead ECG. • A "summary ECG" is a continuously recorded ECG of longer than 10 seconds. For a "summary ECG," the minimal recommended duration is 2 minutes or longer, and the preferred duration is 5 minutes (as it provides the most robust result). If a "summary ECG" is less than 2 minutes, data will still be captured and analyzed to the extent possible. The investigator should review the ECG at screening to determine patient eligibility for the study and subsequent ECGs for the patient's continuation in the study. All ECGs should be reviewed by the investigator for any clinically significant findings during the visit and before the patient leaves the clinic. A qualified physician at Spaulding (the central diagnostic center) will interpret the ECG.	Clarification

Protocol text with changes shown	New wording	Reason/justification for change
The following paragraph was deleted: If a post-treatment QTcF value >500 msec or change from screening or day 1 >60 msec is found, the investigator should repeat the ECG assessment twice and then compare the last pre-treatment QTcF value to the average of the 3 post-treatment QTcF values. TEV-50717 must be stopped for any confirmed post-treatment QTcF average value >500 msec or average increase from screening or day 1 >60 msec.		Clarification
See new wording column	The criteria for an abnormal post-baseline QTcF are a value >500 msec or change from screening >60 msec. If one of these criteria is met, the investigator must further evaluate the QTcF as follows: • If a standard ECG is abnormal and meets the above protocol criteria: o A 5-minute summary ECG recording should be performed at the research site, and a repeat standard ECG is not required. The site should follow the process to have these ECGs read by Spaulding. o If a 5-minute summary ECG cannot be performed (for instance, if patient is evaluated at a facility other than the research site, and the summary ECG is not available), the investigator should obtain 2 repeat standard ECGs and determine the average of these 3 post-screening QTcF values. The site should follow the process to have these ECGs read by Spaulding. • The investigator should then compare the post-screening QTcF values to the pre-treatment QTcF values at screening. As noted above, the post-screening QTcF values will use either the average QTcF from the 3 post-screening standard ECGs or the QTcF from the summary ECG. The IMP must be stopped for any confirmed post-baseline QTcF average value >500 msec or average increase from screening >60 msec.	Clarification

Protocol text with changes shown	New wording	Reason/justification for change
9.1. Sample Size and Power Considerations		
Based on the number of patients in the parent study (Study TEV50717-CNS-30080), ~~up to~~ approximately ~~185~~45 patients ~~(up to a maximum of 230 patients)~~ who completed the parent study may enroll in this study. ~~However, it is expected that approximately 15% of patients enrolled in the parent study will drop out of that study. This sample size is considered sufficient for the exploratory nature of the study.~~	Based on the number of patients in the parent study (Study TEV50717-CNS-30080), to approximately 45 patients who completed the parent study may enroll in this study.	Text revised to account for the change in sample size
9.6. Safety Endpoints and Analysis		
The frequency and severity of suicidal ideation or behavior according to the children's C-SSRS questionnaire will be presented ~~for all patients aged ≥12 years~~ by visit.	The frequency and severity of suicidal ideation or behavior according to the children's C-SSRS questionnaire will be presented by visit.	Clarification
9.7. Efficacy Analysis		
See new wording column	• MD-CRS part I total score (centrally read) • MD-CRS part II total score (centrally read) • UHDRS-TMC (centrally read) • UHDRS-TMD (centrally read)	New secondary endpoints
15. REFERENCES		
The following was deleted: ~~Bethoux F, Fatemi A, Fowler E, Marciniak C, Mayadev A, Waksman J, et al. Safety, tolerability, and sensorimotor effects of extended-release dalfampridine in adults with cerebral palsy: a pilot study. Clin Ther 2017;39(2):337-46.~~ ~~ClinicalTrials.gov. National Library of Medicine (US). Identifier NCT01898520, A Safety, Efficacy and Tolerability Study of Sativex for the Treatment of Spasticity in Children Aged 8 to 18 Years; 2013 Jul 12 [cited 2017 May 17]; Available at: https://clinicaltrials.gov/ct2/show/NCT01898520~~		References deleted to account for the change in sample size and the removal of the second interim analysis as well changes in the introduction

Protocol text with changes shown	New wording	Reason/justification for change
AUSTEDO® (deutetrabenazine) tablets (US prescribing information). Teva Pharmaceuticals USA, Inc; ~~2017~~2021. Available at: https://austedo.com/hd/pi.	AUSTEDO® (deutetrabenazine) tablets (US prescribing information). Teva Pharmaceuticals USA, Inc; 2021. Available at: https://austedo.com/hd/pi.	New USPI since last amendment
APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Row: Sponsor's Authorized Representative Column: [redacted] Teva Pharmaceutical Industries,~~[redacted]~~ [redacted] Cell: [redacted] [redacted]	Row: Sponsor's Authorized Representative Column: [redacted] Teva Pharmaceutical Industries Cell: [redacted] [redacted]	Administrative change
Row: Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study Deleted text: ~~Tel:~~ [redacted]		Administrative change
Row: Sponsor's Representative of Global Patient Safety and Pharmacovigilance Column: [redacted] Teva Pharmaceutical Industries, [redacted] [redacted] Tel: [redacted] Cell: [redacted] [redacted]	Row: Sponsor's Representative of Global Patient Safety and Pharmacovigilance Column: [redacted] Teva Pharmaceutical Industries, [redacted] [redacted] Tel: [redacted] Cell: [redacted] [redacted]	Administrative change
Row: Trial Supply Management ~~(RTSM)~~ vendor Column: ~~PAREXEL International Corp.~~ Calyx ~~195 West Street~~4 Canal Street ~~Waltham, MA 02451~~ Nottingham, United Kingdom, NG1 7EH Tel:~~[redacted]~~	Row: Trial Supply Management vendor Column: Calyx 4 Canal Street Nottingham, United Kingdom, NG1 7EH Tel: [redacted]	Administrative change

Protocol text with changes shown	New wording	Reason/justification for change
Row: Scales and Central ~~Rater for MD-CRS~~ Reading Column: Bracket Global LLC 785 Arbor Way Blue Bell, PA, 19422 Tel : [redacted]	Row: Scales and Central Reading Column: Signant Health 785 Arbor Way Blue Bell, PA 19422 Tel: [redacted]	
APPENDIX C. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
1. Procedures for Screening and Enrollment		
Patients can either enroll in the study at the week 16 visit of Study TV50717-CNS-30080 or up to ~~6 months~~4 weeks following the week 15 visit of Study TV50717-CNS-30080.	Patients can either enroll in the study at the week 16 visit of Study TV50717-CNS-30080 or up to 4 weeks following the week 15 visit of Study TV50717-CNS-30080.	Study procedures and assessments have been updated for consistency with changes made to the protocol body and Tables 4 and 5. This justification applies to all changes indicated within Appendix C.
2.1 Procedures for Patients Who Enroll Between 1 and <2 Weeks After Study TV50717-CNS-30080 Week 15 Visit		
c. Day 1 Assessments		
− Movement Disorder-Childhood Rating Scale (MD-CRS) part I (~~physician~~ centrally read~~, video recording~~) − MD-CRS part II (centrally read) − MD-CRS part I (physician rated, video recording) − MD-CRS part II (physician rated, video recording) − 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) − UHDRS-TMC (physician rated) − UHDRS-TMD (physician rated)	− Movement Disorder-Childhood Rating Scale (MD-CRS) part I (centrally read) − MD-CRS part II (centrally read) − MD-CRS part I (physician rated, video recording) − MD-CRS part II (physician rated, video recording) − 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) − UHDRS-TMC (physician rated) − UHDRS-TMD (physician rated)	

Protocol text with changes shown	New wording	Reason/justification for change
2.2 Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with No Clinically Significant Changes Since the Week 15 Visit of Study TV50717-CNS-30080		
b. Day 1 Assessments		
See new wording column	○ MD-CRS part I (centrally read) ○ MD-CRS part II (centrally read) ○ UHDRS-TMC (centrally read) ○ UHDRS-TMD (centrally read)	
○ UHDRS-TMC (physician rated) ○ UHDRS-TMD (physician rated)	○ UHDRS-TMC (physician rated) ○ UHDRS-TMD (physician rated)	
2.3 Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with Clinically Significant Changes ~~and for Patients Who Enroll More Than 4 Weeks and up to 6 Months After Study TV50717-CNS-30080 Week 15 Visit~~	**2.3 Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with Clinically Significant Changes**	
2.3Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with Clinically Significant Changes		
b. Day 1		
See new wording column	○ MD-CRS part I (centrally read) ○ MD-CRS part II (centrally read) ○ UHDRS-TMC (centrally read) ○ UHDRS-TMD (centrally read)	
○ UHDRS-TMC (physician rated) ○ UHDRS-TMD (physician rated)	○ UHDRS-TMC (physician rated) ○ UHDRS-TMD (physician rated)	

Protocol text with changes shown	New wording	Reason/justification for change
3. Procedures During TEV-50717 Treatment		
a. Titration Period (Weeks 1 to 7)		
ii. In-clinic Visits (Weeks 3 and 7)		
• assess ~~drug~~TEV-50717 accountability/compliance/supply (Note: At the week 3 in-clinic visit, accountability will be performed on all bottles returned except for patients who receive 1 bottle back to complete the week 3 in-clinic evening dose. Refer to the pharmacy manual for further details.)	• assess TEV-50717 accountability/compliance/supply (Note: At the week 3 in-clinic visit, accountability will be performed on all bottles returned except for patients who receive 1 bottle back to complete the week 3 in-clinic evening dose. Refer to the pharmacy manual for further details.)	
b. Maintenance Period (Weeks 14 to 53/Early Termination)		
i. In-clinic Visits (Weeks 14, 27, 40, and 53/Early Termination)		
See new wording column	− MD-CRS part I (centrally read) at weeks 27 and 53/ET − MD-CRS part II (centrally read) at weeks 27 and 53/ET − UHDRS-TMC (physician rated) at weeks 27 and 53/ET − UHDRS-TMD (physician rated) at weeks 27 and 53/ET	
− UHDRS-TMC (physician rated) − UHDRS-TMD (physician rated)	− UHDRS-TMC (physician rated) − UHDRS-TMD (physician rated)	
ii.Telephone Contacts (Weeks 21, 33, and 46)		
If additional ~~drug~~TEV-50717 is required, it would be ordered from the distributor and provided to the patient at an unscheduled visit.	If additional TEV-50717 is required, it would be ordered from the distributor and provided to the patient at an unscheduled visit.	
4. Procedures After TEV-50717 Treatment (Follow-Up)		
a. In-clinic Visit (Week 54)		
See new wording column	− MD-CRS part I (centrally read) − MD-CRS part II (centrally read) − UHDRS-TMC (centrally read) − UHDRS-TMD (centrally read)	

Protocol text with changes shown	New wording	Reason/justification for change
b. Telephone Contact (Week 55)		
The following was deleted: • CGI-I (Note: 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.)		
5. Unscheduled Visits		
• assess drug~~TEV-50717~~ accountability/compliance/supply	• assess TEV-50717 accountability/compliance/supply	
APPENDIX I. TOTAL BLOOD VOLUME		
Patients experiencing an adverse event leading to discontinuation of TEV-50717, or experiencing any other adverse event ~~at the discretion of the investigator~~, should have a single blood sample collected as soon as possible ~~after the adverse event and within 48 hours~~ 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.	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- 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.	
APPENDIX M. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19		
The changes specified in this appendix will be effective for the duration of the COVID-19 pandemic ~~when~~. Once the situation at specific sites/countries will allow returning to regular study activities, this appendix will become void for those country/sites, except in the case of COVID-19 resurgence or emergence of another crisis (eg, geopolitical situation) affecting normal per-protocol conduct of the study.	The changes specified in this appendix will be effective for the duration of the COVID-19 pandemic. Once the situation at specific sites/countries will allow returning to regular study activities, this appendix will become void for those country/sites, except in the case of COVID-19 resurgence or emergence of another crisis (eg, geopolitical situation) affecting normal per-protocol conduct of the study.	Text revised due to the ongoing, changing nature of the COVID-19 pandemic

Protocol text with changes shown	New wording	Reason/justification for change
See new wording column	**Audit and Inspection** In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be audited remotely where allowed and in accordance with local regulations.	Update

16.2. Administrative Letter 06 Dated 11 June 2021

ADMINISTRATIVE LETTER 06

Study number: TV50717-CNS-30081

Clinical Study Protocol with Amendment 03

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)

Version date 23 June 2020

IND number: 139700; EudraCT number: 2019-001807-19

11 June 2021

Dear Investigator:

The purpose of this letter is to clarify details in the Study Protocol on study drug storage temperature requirements, dosage adjustments, discontinuation of dosing at the end of treatment visit, and to correct the date of Letter of Clarification 02.

1. In **Section 5.2.1 Storage and Security** of the Study Protocol, it is stated that "TEV-50717 must be stored at a controlled room temperature, 20°C to 25°C (68°F to 77°F), in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff." In Section 5.1.1.2, Table 8 (bottom row), it is stated that the IMP is to be "Stored at controlled room temperature, 20°C-25°C (68°F-77°F)".

   In addition, in **Section 10** of the Pharmacy Manual, Version 4.1, it is stated "Per the label, the storage conditions are 20°C to 25°C (68°F to 77°F) however excursions permitted 15°C to 20°C (59°F to 68°F) with no need to report. All temperature excursions below 15°C (59°F) or above 25°C (77°F) should be reported to your CRA."

   The sponsor would like to hereby clarify that temperature excursions between 15° to 20°C do not need to be reported, as stated in the pharmacy manual. This clarification will be added to the aforementioned sections of the Study Protocol via a reference to the Pharmacy Manual as follows:

   Section 5.2.1 Storage and Security:

   "TEV-50717 must be stored at a controlled room temperature, 20°C to 25°C (68°F to 77°F), in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff. **For additional information related to IMP storage conditions please refer to Section 10 of the Pharmacy Manual**."

   Section 5.1.1.2, Table 8:

   A footnote will be added to Table 8 with attention to storage conditions as follows: "**For additional information related to IMP storage conditions please refer to Section 10 of the Pharmacy Manual.**"

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2. **Section 5.1.1.2** of the Study Protocol, states "During the titration period, the dose of IMP should be adjusted according to Table 6 to identify a dose level that optimally reduces dyskinesia (as determined by the investigator, as indicated by a reduction in the CGI-I) and is well tolerated". Study Procedures and Assessments (Table 5) identifies that IMP dose evaluations/adjustments occur at the specified remote and in-clinic visits. In alignment with clarifications made to Clinical Study Protocol with Amendment 04 Study TV50717-CNS-30080 in Protocol Administrative Letter 07, the sponsor wishes to clarify and ensure that study drug dose adjustments are made on the day following a phone call visit or site visit. Therefore, the following footnote will be added to Table 6 and to scheduled "in-clinic visits" and "telephone contacts" during the titration period in Table 5: "**All IMP adjustments are made only after a remote or in-clinic visit; if the dose is escalated, the dose escalation will occur with the next morning's dose**".
3. **Section 5.4** of the Study Protocol states "All patients will discontinue TEV-50717 at the week 53 visit and will return 1 week later (week 54) for evaluation of safety". In alignment with clarifications made to Clinical Study Protocol with Amendment 04 Study TV50717-CNS-30080 in Protocol Administrative Letter 07, the sponsor would like to clarify that while discontinuation of study drug will occur at the week 53 visit, dosing regimen may vary for different patients, such that the last dose may be taken by different patients at different times. To account for this variation, the beginning of Section 5.4 will be revised as follows: "**All patients should continue their usual treatment regimen up to week 53 visit (i.e. 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".
4. **Section 16.4** of the Study Protocol presents Letter of Clarification 02 Dated 02 July 2019. To align with the Letter of Clarification date of 1 July 2019, the heading for this section will be corrected to: "Letter of Clarification 02 Dated ~~**02**~~ **01** July 2019".

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

Teva Pharmaceuticals

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16.3. Administrative Letter 05 Dated 23 February 2021

ADMINISTRATIVE LETTER 05

Study number: TV50717-CNS-30081

Clinical Study Protocol with Amendment 03

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)

Version date 23 June 2020

IND number: 139700; EudraCT number: 2019-001807-19

23 February 2021

Dear Investigator:

The purpose of this letter is to reflect a change made to the paragraph describing the efficacy and safety scales evaluation and to clarify the blood sampling timepoints following the onset of an adverse event described in the Study Protocol Body.

1) In Section 6, "Assessment of Efficacy" of the Study Protocol, the phrase "and any trends observed throughout the study" should be removed from the following sentence to clarify the efficacy scales evaluation: "At each study visit, as applicable, the investigator should compare the current scores to the baseline scores ~~and any trends observed throughout the study~~" This also applies to Section 7.2, "Safety Rating Scales" of the Study Protocol (old text is marked with a strikethrough):

Section 6, Assessment of Efficacy

The investigator should review all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly. At each study visit, as applicable, the investigator should compare the current scores to the baseline scores ~~and any trends observed throughout the study~~.

Section 7.2, Safety Rating Scales

The investigator should review all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly. At each study visit, as applicable, the investigator should compare the current scores to the baseline scores ~~and any trends observed throughout the study.~~

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2) In order to clarify the blood sampling timepoints following the onset of an adverse event, the text has been revised as follows (new text is marked in bold and underlined):

"Patients experiencing an adverse event leading to discontinuation of TEV-50717 or experiencing any other adverse event, at the discretion of the investigator, should have a single blood sample collected 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**, for the measurement of TEV-50717, α- and β-HTBZ concentrations, if possible. 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."

The changes will be implemented in the following sections:

Section 3.5, Schedule of Study Procedures and Assessments, Table 5, footnote "s"

Section 4.3, Withdrawal Criteria and Procedures for the Patient

Appendix I ,Total Blood Volume, footnote "c"

Section 3.5, Schedule of Study Procedures and Assessments , Table 5, footnote "s"

[s] Patients experiencing an adverse event leading to discontinuation of TEV-50717 or experiencing any other adverse event, at the discretion of the investigator, should have a single blood sample collected 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**, for the measurement of TEV-50717, α- and β-HTBZ concentrations, if possible. 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.

Section 4.3, Withdrawal Criteria and Procedures for the Patient

Patients experiencing an adverse event leading to discontinuation of TEV-50717, or experiencing any other adverse event at the discretion of the investigator, should have a single blood sample collected 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**, for the measurement of TEV-50717, α-HTBZ and β-HTBZ concentrations, if possible. 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.

Appendix I, Total Blood Volume, footnote "c"

[c] Patients experiencing an adverse event leading to discontinuation of TEV-50717, or any other adverse event at the discretion of the investigator, should have a single blood sample collected 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**, for the measurement of TEV-50717, and α- and β-HTBZ concentrations, if possible. 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. ¶

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

Teva Pharmaceuticals

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16.4. Administrative Letter 04 Dated 14 November 2020

ADMINISTRATIVE LETTER 04

Study number: TV50717-CNS-30081

Clinical Study Protocol with Amendment 03

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)

Version date 23 June 2020

IND number: 139700; EudraCT number: 2019-001807-19

14 November 2020

Dear Investigator:

The purpose of this letter is to align the language of Appendix M to the language utilized in the Study Protocol Body.

In Appendix M, "Management of Study Activities During COVID-19" of the Study Protocol, the term "FaceTime® (Apple Inc)" should be changed to "non-recording live video". This applies to Section 6, "Assessments of Efficacy" and to Section 7.2 "Safety Rating Scales" of the Study Protocol listed in Appendix M. New text is marked in bold and underlined.

Section 6 Assessments of Efficacy

In the event of an emergency situation (eg, the COVID-19 pandemic), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), remote assessment may be allowed for the following:

- via **non-recording live video** ~~FaceTime® (Apple Inc)~~ for the Clinical Global Impression of Improvement [CGI-I] mandatory at week 3 and week 7, Clinical Global Impression of Severity [CGI-S], Movement Disorder-Childhood Rating Scale [MD-CRS] parts I and II, Unified Huntington's Disease Rating Scale-Total Motor Score [UHDRS-TMS], and the Canadian Occupational Performance Measure [COPM], as applicable. The results of the questionnaires will be entered to the case report form (CRF) per the usual process indicating that the rating has been performed remotely.
- via iPhone® (Apple, Inc) or via paper back-up copy instead of iPad® (Apple Inc) for the Caregiver Global Impression of Improvement [CaGI-I] and the Pediatric Evaluation Disability Inventory-Computer Adapted Test [PEDI-CAT], as applicable. The results of the questionnaires will be transferred to the CRF per the usual process (either from iPhone or from paper back-up copy).

The MD-CRS Part I & II are optional at the investigator's discretion and may be incomplete considering patient's imbalance when standing and walking and prioritizing patient safety. UHDRS-TMS should be completed as much as possible; some fields (ie, rigidity, stability) may be left blank as they cannot be assessed remotely. The pull test should not be done due to safety considerations.

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Section 7.2 Safety Rating Scales

In the event of an emergency situation (eg, the COVID-19 pandemic), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), remote assessment of safety scales may be allowed for the following:

- via a phone call, supported by **non-recording live video** ~~FaceTime®~~ for the C-SSRS (mandatory) and for the Extrapyramidal Symptom Rating Scale (ESRS), which should be completed as much as possible; some fields [ie, rigidity, stability] may be

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

Teva Pharmaceuticals

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16.5. Administrative Letter 03 Dated 14 July 2020

ADMINISTRATIVE LETTER 03[1]

Study number: TV50717-CNS-30081

Clinical Study Protocol with Amendment 3

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), Dated 23 June 2020

IND Number: 139700; EudraCT Number: 2019-001807-19

14 July 2020

Dear Investigator:

The purpose of this letter is to clarify that the IWRS is *not* contacted at screening for patients:

- who enroll in the study between 2 to ≤4 weeks after Study TV50717-CNS-30080 week 15 visit and who 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

  OR

- who enroll in the study more than 4 weeks and up to 6 months after Study TV50717-CNS-30080 week 15 visit.

The changes are included below with ~~blue strikethrough~~ indicating deleted text.

Old wording			New wording		
3.5. Schedule of Study Procedures and Assessments					
Table 4: Study Procedures and Assessments: Screening and/or Day 1					
	Day 1 **Between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit and with clinically significant changes[b]** **OR** **Day 1** **More than 4 weeks and up to 6 months after Study TV50717-CNS-30080 week 15 visit**			**Day 1** **Between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit and with clinically significant changes[b]** **OR** **Day 1** **More than 4 weeks and up to 6 months after Study TV50717-CNS-30080 week 15 visit**	
Study day	**Screening**	**Day 1/BL (within 31 days from screening)**	**Study day**	**Screening**	**Day 1/BL (within 31 days from screening)**
Contact IWRS	~~X~~	X	Contact IWRS		X

[1] Previously referred to as a "Letter of Clarification"

Old wording	New wording
APPENDIX C. STUDY PROCEDURES AND ASSESSMENTS BY VISIT	
2. Procedures Before TEV-50717 Treatment	
2.3 Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with Clinically Significant Changes and for Patients Who Enroll More Than 4 Weeks and up to 6 Months After Study TV50717-CNS-30080 Week 15 Visit	
a. Screening • ~~contact IWRS~~	a. Screening

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] at either [redacted] or [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted] Teva Pharmaceuticals

16.6. Amendment 03 Dated 23 June 2020

The primary reason for this amendment is to provide the management of COVID-19 pandemic-related operational updates as detailed in a new appendix (Appendix M).

This amendment is considered to be substantial by the sponsor's authorized representative. These substantive changes included the addition of video recording of the MD-CRS assessment. The MD-CRS video recording was added to this amendment as the video is a recognized component of the MD-CRS.

All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Minor or editorial non-substantial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Protocol text with changes shown	New wording	Reason/Justification for change
3.1. General Study Design and Study Schematic Diagram		
Site-administered scales include the Movement Disorder-Childhood Rating Scale (MD-CRS) parts I and II (physician rated, with video recording)…	Site-administered scales include the Movement Disorder-Childhood Rating Scale (MD-CRS) parts I and II (physician rated, with video recording)…	MD-CRS video recording added as recognized part of the assessment.
• ~~vital signs (respiratory rate and body temperature) and~~ weight is~~are~~ performed at week 16 in Study TV50717-CNS-30080 and height is performed at week 15 in study TV50717-CNS-30080; these assessments will serve as day 1 baseline values in this study. • vital signs (respiratory rate and body temperature) are performed at week 16 in 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, these assessments will serve as day 1 baseline values in this study. Otherwise, these assessments will be performed at day 1.	• weight is performed at week 16 in Study TV50717-CNS-30080 and height is performed at week 15 in study TV50717-CNS-30080; these assessments will serve as day 1 baseline values in this study. • vital signs (respiratory rate and body temperature) are performed at week 16 in 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, these assessments will serve as day 1 baseline values in this study. Otherwise, these assessments will be performed at day 1.	Clarification
See New Wording Column	For corona virus disease 2019 (COVID-19) updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
3.2. Planned Number of Patients and Regions		
The study is expected to start by the end of Q1 2020 and last until ~~Q4 2022~~Q2 2023.	The study is expected to start by the end of Q1 2020 and last until Q2 2023.	
3.3. Justification for Study Design and Selection of Population		
The study population will include pediatric and adolescent patients (6 through 18+ years of age at the time when they enrolled in the parent study [Study TV50717-CNS-30080]), ie, 6 through 20 years of age when they enroll in TV50717-CNS-30081 study, with DCP with predominant choreiform movement disorder, who have had non-progressive CP symptoms since infancy (≤2 years of age), and have completed Study TV50717-CNS-30080.	The study population will include pediatric and adolescent patients (6 through 18+ years of age at the time when they enrolled in the parent study [Study TV50717-CNS-30080]), ie, 6 through 20 years of age when they enroll in TV50717-CNS-30081 study, with DCP with predominant choreiform movement disorder, who have had non-progressive CP symptoms since infancy (≤2 years of age), and have completed Study TV50717-CNS-30080.	Clarification
3.5. Schedule of Study Procedures and Assessments		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M

Protocol text with changes shown	New wording	Reason/Justification for change
Table 4 Study Procedures and Assessments: Screening and/or Day 1		
See New Wording Column	Table 4 has been revised as described below: • Video recording added to both MD-CRS Part I and Part II • CBCL has been added to screening visit • Footnotes revised/added to clarify which CBCL assessments are completed at day 1 and screening, to clarify when vital signs are to be performed, and to add the video recording to the MD-CRS assessments	Revisions were incorporated to clarify and align Table 4 with Appendix C (Section 2.3), to clarify when vital signs will be performed, and to add MD-CRS video recording as a recognized part of the assessment.
Table 5 Study Procedures and Assessments: Titration, Maintenance, and Follow-up Periods		
See New Wording Column	Table 5 has been revised as described below: • Video recording added to both MD-CRS Part I and Part II • Footnotes revised/added to add video recording for MD-CRS	MD-CRS video recording added as recognized part of the assessment.
4.3. Withdrawal Criteria and Procedures for the Patient		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
5.1.1.2. Dose Modification and Dose Stratification		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
5.2. Preparation, Handling, Labeling, Storage, and Accountability for IMPs		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
5.11 Total Blood Volume		
The total blood volume to be collected for each patient in this study is approximately ~~76~~77.5 mL.	The total blood volume to be collected for each patient in this study is approximately 77.5 mL.	Clarification
6. ASSESSMENT OF EFFICACY		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference

Protocol text with changes shown	New wording	Reason/Justification for change
		the addition of Appendix M
6.1.1. Movement Disorder-Childhood Rating Scale		
The MD-CRS (with video recording) will be administered at the day 1 visit (Table 4) and at week 14, week 27, week 40, week 53/ET, and week 54/follow-up visits (Table 5).	The MD-CRS (with video recording) will be administered at the day 1 visit (Table 4) and at week 14, week 27, week 40, week 53/ET, and week 54/follow-up visits (Table 5).	MD-CRS video recording added as recognized part of the assessment.
7. ASSESSMENT OF SAFETY		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
7.2. Safety Rating Scales		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
7.2.3. Child Behavior Checklist (for Ages 6 to 18)		
The full CBCL assessment (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) will be completed at the screening or day 1 visit, as applicable (Table 4) and at the week 53/ET visit (Table 5). The Syndrome Scale part of the CBCL [behavioral items] will be completed at day 1, as applicable (Table 4) and at weeks 3, 7, 14, 27, 40, and 54/follow-up visits (Table 5).	The full CBCL assessment (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) will be completed at the screening or day 1 visit, as applicable (Table 4) and at the week 53/ET visit (Table 5). The Syndrome Scale part of the CBCL [behavioral items] will be completed at day 1, as applicable (Table 4) and at weeks 3, 7, 14, 27, 40, and 54/follow-up visits (Table 5).	Revisions were incorporated to clarify and align with Appendix C
7.2.4. Epworth Sleepiness Scale (for Children and Adolescents		
The ESS is administered at the screening and/or day 1 visit, as applicable (Table 4) and administered at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits (Table 5).	The ESS is administered at the screening and/or day 1 visit, as applicable (Table 4) and administered at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits (Table 5).	Revisions were incorporated to clarify and align with Table 4
7.5. Clinical Laboratory Tests		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
7.5.1. Serum Chemistry, Hematology, and Urinalysis		
Clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis) will be performed at the time points detailed in Table 4 and Table 5 (ie, screening and weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits). Clinical	Clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis) will be performed at the time points detailed in Table 4 and Table 5 (ie, screening and weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits).	Revisions were incorporated to clarify and align with Table 4

Protocol text with changes shown	New wording	Reason/Justification for change
laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided in Table 10.	Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided in Table 10.	
7.5.2.2. Urine Drug Screen		
Some of the drugs or drug classes listed in this urine drug screen may be permitted in certain cases in which the particular drug or drug class is being used under a physician's or clinician's guidance and in compliance with the physician's/clinician's recommendation for a specific condition; for example, phenobarbital (barbiturates) for seizures, ~~stimulant medications (including~~ amphetamines~~, methylphenidate, and lisdexamfetamine)~~ for attention deficit hyperactivity disorder, and opiates or oxycodone for pain, if the dosing has been stable for at least 4 weeks before screening or day 1 and if no changes to dose or frequency are anticipated during the course of the study.	Some of the drugs or drug classes listed in this urine drug screen may be permitted in certain cases in which the particular drug or drug class is being used under a physician's or clinician's guidance and in compliance with the physician's/clinician's recommendation for a specific condition; for example, phenobarbital (barbiturates) for seizures, amphetamines for attention deficit hyperactivity disorder, and opiates or oxycodone for pain, if the dosing has been stable for at least 4 weeks before screening or day 1 and if no changes to dose or frequency are anticipated during the course of the study.	Text clarified to provide examples of some drug classes that might be prescribed and possibly be identified on the urine drug screen; some of the mentioned drugs may not be identified on urine drug screen
7.6. Vital Signs		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
7.9. Electrocardiography		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
9. Statistics		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
10. Quality Control and Quality Assurance		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
Appendix C. Study Procedures And Assessments By Visit		
2. Procedures Before TEV-50717 Treatment		
2.1 Procedures for Patients Who Enroll Between 1 and <2 Weeks After Study TV50717-CNS-30080 Week 15 Visit		

Protocol text with changes shown	New wording	Reason/Justification for change
b. Assessments carried over from Study TV50717-CNS-30080 - Week 15/16		
• W16 vital signs (body temperature and respiratory rate). 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, these assessments will serve as day 1 baseline values in this study. Otherwise, these assessments will be performed at day 1.	• W16 vital signs (body temperature and respiratory rate). 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, these assessments will serve as day 1 baseline values in this study. Otherwise, these assessments will be performed at day 1.	Clarification
c. Day 1 Assessments		
• administer the following assessments: – Movement Disorder-Childhood Rating Scale (MD-CRS) part I (physician rated, video recording) – MD-CRS part II (physician rated, video recording)	• administer the following assessments: – Movement Disorder-Childhood Rating Scale (MD-CRS) part I (physician rated, video recording) – MD-CRS part II (physician rated, video recording)	MD-CRS video recording added as recognized part of the assessment.
2.2 Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with No Clinically Significant Changes Since the Week 15 Visit of Study TV50717-CNS-30080		
b. Day 1 Assessments		
• vital signs (orthostatic pulse, and BP, body temperature, and respiratory rate)	• vital signs (orthostatic pulse and BP, body temperature, and respiratory rate)	Clarification
• MD-CRS part I (physician rated, video recording) • MD-CRS part II (physician rated, video recording)	• MD-CRS part I (physician rated, video recording) • MD-CRS part II (physician rated, video recording)	MD-CRS video recording added as recognized part of the assessment.
2.3. Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with Clinically Significant Changes and for Patients Who Enroll More Than 4 Weeks and up to 6 Months After Study TV50717-CNS-30080 Week 15 Visit		
a. Screening		
See New Wording Column	• ESS (for children and adolescents)	Revisions were incorporated to clarify and align with Table 4
b. Day 1		
• vital signs (orthostatic pulse, and BP, body	• vital signs (orthostatic pulse and BP, body	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
temperature, and respiratory rate)	temperature, and respiratory rate)	
• MD-CRS part I (physician rated, video recording) • MD-CRS part II (physician rated, video recording)	• MD-CRS part I (physician rated, video recording) • MD-CRS part II (physician rated, video recording)	MD-CRS video recording added as recognized part of the assessment.
3. Procedures During TEV-50717 Treatment		
i. In-clinic Visits (Weeks 14, 27, 40, and 53/Early Termination)		
• administer the following assessments: – MD-CRS part I (physician rated, video recording) – MD-CRS part II (physician rated, video recording)	• administer the following assessments: – MD-CRS part I (physician rated, video recording) – MD-CRS part II (physician rated, video recording)	MD-CRS video recording added as recognized part of the assessment.
4. Procedures After TEV-50717 Treatment (Follow-Up)		
a. In-clinic Visit (Week 54)		
• administer the following assessments: – MD-CRS part I (physician rated, video recording) – MD-CRS part II (physician rated, video recording)	• administer the following assessments: – MD-CRS part I (physician rated, video recording) – MD-CRS part II (physician rated, video recording)	MD-CRS video recording added as recognized part of the assessment.
Appendix D. Quality Control and Quality Assurance		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
Appendix H. List of Allowed and Prohibited Medications		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated section to cross-reference the addition of Appendix M
Appendix I. Total Blood Volume		
Total blood volume to be collected for each patient in this study is approximately ~~76~~77.5 mL.	Total blood volume to be collected for each patient in this study is approximately 77.5 mL.	Clarification
See New Wording Column	The table has been revised as described below: • The total blood volume for each visit has been updated	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
	Footnote has been deleted	
Appendix M. Management of Study Activities During COVID-19		
See New Wording Column	Additional text too numerous to include in this table; refer to Appendix M of this protocol.	Updated to manage study conduct during the COVID-19 pandemic.

16.7. Amendment 02 Dated 19 March 2020

The primary reason for this amendment is to extend the rolling-over period from the parent Study TV50717-CNS-30080 to the open-label safety extension Study TV50717-CNS-30081.

This amendment is considered to be substantial by the sponsor's authorized representative. These substantive changes included revised inclusion and exclusion criteria, changes to the allowed and prohibited medications, and updates to the general study design. Table 4 and Figure 2 were included to provide further clarification and support the more significant adjustments to the study design. Table 5 (Study Procedures and Assessments: Titration, Maintenance, and Follow-up Periods) has been revised to reflect agreed changes to the study design. All of the changes in the table below reflect what has changed from Amendment 01.

Other minor or editorial non-substantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Protocol text with changes shown	New wording	Reason/Justification for change
Title page (Other sections affected by these changes: Synopsis)		
Teva Branded Pharmaceutical Products R&D, Inc. ~~41 Moores Road~~145 Brandywine Parkway West Chester~~Frazer~~, Pennsylvania 19380~~55~~ United States of America	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, Pennsylvania 19380 United States of America	New sponsor address
SYNOPSIS (Planned Study Period)		
~~Q4 2019~~Q1 2020-to Q4 2022 with a duration of approximately 55 weeks	Q1 2020-to Q4 2022 with a duration of approximately 55 weeks	Clarification
SYNOPSIS (Plans for Treatment or Care after the Patient Has Ended Participation in the Study)		
~~There is no treatment or care planned for patients after the end of the study.~~ There are no plans to provide further treatment to patients upon completion of the study. An extension to the study may be considered on an annual basis.	There are no plans to provide further treatment to patients upon completion of the study. An extension to the study may be considered on an annual basis.	Clarification of the potential plans for patient treatment upon completion of the study
1.1. Introduction		
Dyskinesia in cerebral palsy (DCP) is a ~~hyperkinetic movement disorder~~ form of CP characterized by abnormal involuntary movements of the dystonic and choreiform types in approximately 6% to 15% of patients with CP.	Dyskinesia in cerebral palsy (DCP) is a form of CP characterized by abnormal involuntary movements of the dystonic and choreiform types in approximately 6% to 15% of patients with CP.	Clarification
Prematurity is the most common cause of CP, but other causes include stroke, hypoxic ischemic injury, infection, ~~and~~ brain malformation, and genetic abnormalities (CDC Causes and Risk Factors of Cerebral Palsy 2018; NINDS Cerebral Palsy: Hope Through Research 2019).	Prematurity is the most common cause of CP, but other causes include stroke, hypoxic ischemic injury, infection, brain malformation, and genetic abnormalities (CDC Causes and Risk Factors of Cerebral Palsy 2018; NINDS Cerebral Palsy: Hope Through Research 2019).	Clarification
2.1.Primary and Secondary Study Objectives and Endpoints		
See New Wording Column	• UHDRS-TMC (physician rated) • UHDRS-TMD (physician rated) UHDRS-TMC=Unified Huntington's Disease Rating Scale-Total Maximal Chorea; UHDRS-TMD=Unified Huntington's Disease Rating Scale-Total Maximal Dystonia.	The table in this section has been revised to add two new secondary objectives and to add to the list of abbreviations

Protocol text with changes shown	New wording	Reason/Justification for change
3.1.General Study Design and Study Schematic Diagram		
For patients rolling over from Study TV50717-CNS-30080, the week 16 visit ~~will~~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 ~~1 week~~6 months following the week 15~~6~~ visit of the TV50717-CNS-30080 study. Any patient who cannot enroll within this timeframe, for any justified reason, must be discussed and pre-approved by the medical monitor prior to enrolling the patient. The end of study TV50717-CNS-30081 is defined as the date of the week 55 follow-up telephone contact of the last participant.	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 6 months following the week 15 visit of the TV50717-CNS-30080 study. Any patient who cannot enroll within this timeframe, for any justified reason, must be discussed and pre-approved by the medical monitor prior to enrolling the patient. The end of study TV50717-CNS-30081 is defined as the date of the week 55 follow-up telephone contact of the last participant.	Clarification on timing of enrollment and informed consent/assent process
Informed consent/assent, as appropriate, based on the ~~child's~~ 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 procedure is performed. Informed consent/assent ~~should be obtained at day 1 of Study TV50717-CNS-30081; however,~~ process can begin within 4 weeks before possible participation in the open label study to allow patients adequate time to engage and ask questions. ~~Informed consent/assent 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.~~	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 procedure is performed. 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.	Clarification on timing of enrollment and informed consent/assent process
For patients who are minors, the caregiver is typically a parent or ~~legal guardian~~legally acceptable representative. In some countries, an adult (such as grandparent or nurse) ~~can~~may be appointed by the parent or ~~legal guardian~~ legally acceptable representative (as per local regulations and laws) and would take over this responsibility as caregiver. The parent or ~~legal guardian~~ legally acceptable representative only has to sign the parent/~~legal guardian~~legally acceptable representative informed consent form (ICF) and not the caregiver ICF.	For patients who are minors, the caregiver is typically a parent or legally acceptable representative. In some countries, an adult (such as grandparent or nurse) may be appointed by the parent or legally acceptable representative (as per local regulations and laws) and would take over this responsibility as caregiver. The parent or legally acceptable representative only has to sign the parent/legally acceptable representative informed consent form (ICF) and not the caregiver ICF.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
For adult patients, a caregiver must be appointed by the patient~~;~~. The caregiver~~this~~ can be the parent or other adult as appropriate and according to local laws and regulations.	For adult patients, a caregiver must be appointed by the patient. The caregiver can be the parent or other adult as appropriate and according to local laws and regulations.	Clarification
For patients who are minors, certain responsibilities in the protocol can only be completed by the parent/~~legal guardian~~legally acceptable representative, ie, informed consent, withdrawal of consent, requests for discontinuation of IMP, or withdrawal from the study for any reason. To further clarify, the caregiver is not allowed to make decisions on the child's health, or where "parent/~~legal guardian~~legally acceptable representative" is specifically indicated in the protocol.	For patients who are minors, certain responsibilities in the protocol can only be completed by the parent/legally acceptable representative, ie, informed consent, withdrawal of consent, requests for discontinuation of IMP, or withdrawal from the study for any reason. To further clarify, the caregiver is not allowed to make decisions on the child's health, or where "parent/legally acceptable representative" is specifically indicated in the protocol.	Clarification
… Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS), Unified Huntington's Disease Rating Scale-Total Maximal Chorea (UHDRS-TMC), Unified Huntington's Disease Rating Scale-Total Maximal Dystonia (UHDRS-TMD), Canadian Occupational Performance Measure (COPM)…	… Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS), Unified Huntington's Disease Rating Scale-Total Maximal Chorea (UHDRS-TMC), Unified Huntington's Disease Rating Scale-Total Maximal Dystonia (UHDRS-TMD), Canadian Occupational Performance Measure (COPM)…	Revised to add two new secondary objectives
See New Wording Column	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 (Figure 2).	Clarification
Day 1: Between 1 and <2 weeks after Study TV50717-CNS-30080 week 15 visit: ~~Screening: Screening evaluations for this open-label study will be performed as part of the baseline 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. ~~Any adverse event that started after the end of the parent study and is recorded after informed consent/assent for this open-label study will be captured within this study baselinevisit.~~	**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, electrocardiogram (ECG), beta-human chorionic	Clarification of the timing of enrollment and subsequent assessments required/carried over from the parent study based on the window of time when the patient rolled into the open-label extension study

Protocol text with changes shown	New wording	Reason/Justification for change
~~Day 1 visit: For all patients, the week 16 visit from Study TV50717-CNS-30080 may be the day 1 visit for Study TV50717-CNS-30081.~~ 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, electrocardiogram (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.	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.	
• Urine drug screen is performed at week 16 in study TV50717-CNS-30080 and will serve as day 1 baseline values in this study. • 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. • vital signs (respiratory rate and body temperature) and weight are performed at week 16 in Study TV50717-CNS-30080 and height is performed at week 15 in study TV50717-CNS-30080; these ~~findings~~assessments will serve as day 1 baseline values in this study. • physical and neurological examinations are performed at week 15 (and week 16, if applicable) in Study TV50717-CNS-30080. The findings from the last assessment taken will serve as day 1 baseline values in this study. • ECG is to be performed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. • medical and psychiatric history are to be assessed on day 1	• Urine drug screen is performed at week 16 in study TV50717-CNS-30080 and will serve as day 1 baseline values in this study. • 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. • vital signs (respiratory rate and body temperature) and weight are performed at week 16 in Study TV50717-CNS-30080 and height is performed at week 15 in study TV50717-CNS-30080; these assessments will serve as day 1 baseline values in this study. • physical and neurological examinations are performed at week 15 (and week 16, if applicable) in Study TV50717-CNS-30080. The findings from the last assessment taken will serve as day 1 baseline values in this study. • ECG is to be performed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. • medical and psychiatric history are to be assessed on	Clarification of the timing of enrollment and subsequent assessments required/carried over from the parent study based on the window of time when the patient rolled into the open-label extension study

Protocol text with changes shown	New wording	Reason/Justification for change
of Study TV50717-CNS- 30081 and will serve as day 1 baseline values in this study. • COPM (an assessment included only in Study TV50717-CNS-30081) will also be performed at day 1.	day 1 of Study TV50717-CNS- 30081 and will serve as day 1 baseline values in this study. • COPM (an assessment included only in Study TV50717-CNS-30081) will also be performed at day 1.	
See New Wording Column	**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 4, 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 4. 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. For patients who enroll in the study between 2 and ≤4 weeks after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.	Clarification of the timing of enrollment and subsequent assessments required/carried over from the parent study based on the window of time when the patient rolled into the open-label extension study

Protocol text with changes shown	New wording	Reason/Justification for change
See New Wording Column	**Day 1: More than 4 weeks and up to 6 months after Study TV50717-CNS-30080 week 15 visit:** The patient will undergo all screening procedures outlined in Table 4. 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. For patients who enroll in the study more than 4 weeks and up to 6 months after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.	Clarification of the timing of enrollment and subsequent assessments required/carried over from the parent study based on the window of time when the patient rolled into the open-label extension study
The dose of ~~the~~ TEV-50717 should be increased ~~on a weekly basis~~ to reach a clinically meaningful reduction in dyskinesia, as indicated by a reduction in the CGI-I (see Table 6). … • the maximum allowable dose is reached based on the patient's weight and CYP2D6 impairment status at day 1. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor.	The dose of TEV-50717 should be increased to reach a clinically meaningful reduction in dyskinesia, as indicated by a reduction in the CGI-I (see Table 6). … • the maximum allowable dose is reached based on the patient's weight and CYP2D6 impairment status at day 1. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor.	Clarification
Maintenance period (46 weeks): At the end of the titration period (week 7), the patient's initial dose for the maintenance period (~~week 8~~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 (Table 6 and Table 7).	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 (Table 6 and Table 7).	Revised to include the two newly added secondary objectives
… UHDRS-TMS, UHDRS-TMC, UHDRS-TMD, COPM…	… UHDRS-TMS, UHDRS-TMC, UHDRS-TMD, COPM…	
Study procedures and assessments with their time points are ~~shown~~ presented for screening and/or day 1 in Table 4 and for the titration, maintenance, and follow-up periods in Table	Study procedures and assessments with their time points are presented for screening and/or day 1 in Table 4 and for the titration, maintenance, and follow-up periods in Table 5. The	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
5. 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.	study schematic diagram is presented in Figure 1. A flow chart for patient screening and day 1 visit assessments is presented in Figure 2.	
See New Wording Column	New Figure 2 (Flow Chart for Patient Screening and Day 1 Visit Assessments) has been added	New figure included for clarification around patient rollover expectations
3.2.Planned Number of Patients and Regions		
The study is expected to start by the end of ~~Q4 2019~~Q1 2020 and last until Q4 2022.	The study is expected to start by the end of Q1 2020 and last until Q4 2022.	Clarification to the expected start date of the study
3.3. Justification for Study Design and Selection of Population		
The study population will include pediatric and adolescent patients (6 through 18 years of age~~)~~ at the time when they enrolled in the parent study [Study TV50717-CNS-30080]) with DCP with predominant choreiform movement disorder… Study TV50717-CNS-30081 uses the same versions of scales as in the parent study, to maintain consistency of evaluations between these studies. As such, Study TV50717-CNS-30081 includes some scales that are designated for patients up to 18 years old, although potentially some patients who entered the parent study at age 18 will now be over 18 years old in this extension study.	The study population will include pediatric and adolescent patients (6 through 18 years of age at the time when they enrolled in the parent study [Study TV50717-CNS-30080]) with DCP with predominant choreiform movement disorder.... Study TV50717-CNS-30081 uses the same versions of scales as in the parent study, to maintain consistency of evaluations between these studies. As such, Study TV50717-CNS-30081 includes some scales that are designated for patients up to 18 years old, although potentially some patients who entered the parent study at age 18 will now be over 18 years old in this extension study.	Clarification
3.5. Schedule of Study Procedures and Assessments		
Study procedures and assessments with their time points are presented for screening and day 1 in Table 4 and for the titration, maintenance, and follow-up periods in Table 5.	Study procedures and assessments with their time points are presented for screening and day 1 in Table 4 and for the titration, maintenance, and follow-up periods in Table 5.	Clarification to align with updates to the schedule of assessments tables
See New Wording Column	Table 4 (Study Procedures and Assessments: Screening and/or Day 1) has been added	Table 4 added to provide clarification of assessments carried over or required upon entry to the open-label extension study, based on length of time between completion of parent study and rollover into this study

Protocol text with changes shown	New wording	Reason/Justification for change
Table 5: Study Procedures and Assessments: Titration, Maintenance, and Follow-up Periods		
See New Wording Column	Table 5 has been revised as described below: • Baseline visit, any related baseline-only procedures, and any related footnotes have been removed • UHDRS-TMC and UHDRS-TMD have been added • Contact IWRS has been added for in clinic visits and unscheduled visits • Table footnotes have been adjusted to align with updated study design expectations • List abbreviations has been updated • A general note was included to recommend/indicate that the same order of administration/completion of the scales be kept per patient throughout the study (as best as possible) and to advise on timely review of scales for any potential adverse events that require reporting	Revisions were incorporated to clarify and align Table 5 and its corresponding footnotes against the updates included throughout the study design and body of the protocol
~~f~~c …Patients experiencing an adverse event leading to discontinuation or any other adverse event at the discretion of the investigator of TEV-50717 should have a~~A~~ blood sample collected as soon as possible after the adverse event and within 48 hours for the measurement of TEV-50717, α- and β-HTBZ concentrations ~~should be collected~~, if possible~~, from each patient experiencing a serious adverse event or an adverse event leading to discontinuation of TEV-50717in at any time during the study~~. To permit the assessment of 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.	c …Patients experiencing an adverse event leading to discontinuation or any other adverse event at the discretion of the investigator of TEV-50717 should have a blood sample collected as soon as possible after the adverse event and within 48 hours for the measurement of TEV-50717, α- and β-HTBZ concentrations, if possible. To permit the assessment of 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.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
~~ki~~ 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).	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).	Clarification
g With the exception of patients weighing ≥40 kg (see footnote "c" in Table 6), dose increases may not occur more frequently than every 5 days.	g With the exception of patients weighing ≥40 kg (see footnote "c" in Table 6), dose increases may not occur more frequently than every 5 days.	Clarification
~~l~~i 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 ~~day 1~~W14 and W53/ET.	i 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.	Clarification
~~r~~n. … Children who turn 12 years old during the study will be administered C-SSRS (baseline/screening) as initial assessment during the study.	n. … Children who turn 12 years old during the study will be administered C-SSRS (baseline/screening) as initial assessment during the study.	
See New wording column	p 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.	
See New wording column	s Patients experiencing an adverse event leading to discontinuation of TEV-50717 or experiencing any other adverse event, at the discretion of the investigator, should have a single blood sample collected as soon as possible after the adverse event and within 48 hours for the measurement of TEV-50717, α- and β-HTBZ concentrations, if possible. To permit the assessment of 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.	

Protocol text with changes shown	New wording	Reason/Justification for change
See New wording column	q 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	Footnote added to provide additional guidance to the investigator
~~t~~r 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.	r 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.	Clarification provided around verification of study drug compliance
~~u~~t 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.	t 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.	Clarification
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.	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 note included to provide additional guidance to the investigator surrounding the order of administration and review of scales
4.1. Patient Inclusion Criteria		
Inclusion Criteria: Patients who ~~have completed Study TV50717-CNS-30080 have already met~~ meet the criteria below are eligible to be included in the study. a. Patient has completed week 16 of ~~the~~ ~~parent~~ Study TV50717-CNS-30080	**Inclusion Criteria:** Patients who meet the criteria below are eligible to be included in the study. a. Patient has completed week 16 of Study TV50717-CNS-30080	Clarification
g. For a patient who is a minor, the parent(s)/~~legal guardian~~legally acceptable representative(s) provides written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide written informed consent (in accordance with local regulations) and the legally acceptable	g. For a patient who is a minor, the parent(s)/legally acceptable representative(s) provides written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide written informed consent (in accordance with local regulations) and the legally acceptable representative will sign, if	Text added to provide additional guidance in consideration of exclusion crtieria “i”

Protocol text with changes shown	New wording	Reason/Justification for change
representative will sign, if needed ~~provide their own written informed consent~~. In this study, eligible patients with dyskinetic cerebral palsy may have some degree of mental, motor, and/or communication (eg, speech, writing, etc.) limitations or disabilities. The patient may not be able to read the assent form. Some patients may only be able to provide a limited assent/consent (for instance, by verbalizations or gestures). The investigator will determine the suitability of enrolling such patients in this study and will follow the local requirement to obtain the relevant consent/assent.	needed. In this study, eligible patients with dyskinetic cerebral palsy may have some degree of mental, motor, and/or communication (eg, speech, writing, etc.) limitations or disabilities. The patient may not be able to read the assent form. Some patients may only be able to provide a limited assent/consent (for instance, by verbalizations or gestures). The investigator will determine the suitability of enrolling such patients in this study and will follow the local requirement to obtain the relevant consent/assent.	
h. A caregiver provides written informed consent after being assigned the role by an adult patient or if this role is delegated by the parent/~~legal guardian~~legally acceptable representative of a patient who is a minor.	h. A caregiver provides written informed consent after being assigned the role by an adult patient or if this role is delegated by the parent/legally acceptable representative of a patient who is a minor.	Clarification
4.2. Patient Exclusion Criteria		
a. Patient has clinically significant depression at screening or day 1 of this study. Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening or day 1 (whichever comes first) and anticipated to remain stable (dose and frequency) within the study duration.	b. Patient has clinically significant depression at screening or day 1 of this study. Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening or day 1 (whichever comes first) and anticipated to remain stable (dose and frequency) within the study duration.	Exclusion criteria were revised to provide more clear guidelines for patient exclusion. Specific stipulations and concomitant medications were clarified
b. Patient has a history of suicidal intent or related behaviors based on medical or psychiatric history or the C-SSRS at screening visit, if performed, or at the day 1 visit, as applicable according to the patient's age: – ~~previous~~ intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence, at the time of suicidal thought – ~~previous~~ suicidal preparatory acts or behavior	b. Patient has a history of suicidal intent or related behaviors based on medical or psychiatric history or the C-SSRS at screening visit, if performed, or at the day 1 visit, as applicable according to the patient's age: – intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence, at the time of suicidal thought – suicidal preparatory acts or behavior	Clarification
c. Patient has a history of a previous actual, interrupted, or aborted suicide attempt based on medical or psychiatric history or the C-SSRS at screening visit, if performed, or at the day 1 visit, as applicable according to the patient's	c. Patient has a history of a previous actual, interrupted, or aborted suicide attempt based on medical or psychiatric history or the C-SSRS at screening visit, if performed, or at the day 1 visit, as applicable according to the patient's	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
age.	age.	
~~e. Patient who is currently receiving or who has received botulinum neurotoxin (BoNT) in an investigational clinical trial.~~ ~~Note: Patients may be included in the study if they have at least 2 treatments of Food and Drug Administration-approved BoNT at a regular interval (eg, every 3 to 4 months), in reasonably stable dosages and locations (subject to investigator's judgment) to treat lower limb spasticity or dystonia.~~ ~~"Food and Drug Administration-approved BoNT" is to be defined as an FDA-approved compound, not necessarily an FDA-approved treatment for children. BoNT treatments other than FDA-approved drugs can be~~	Prior exclusion criteria "e" has been removed	Upon further consideration of exlusion criteria "e", it was decided to remove the criteria surrounding BoNT and provide clarification in Appendix H.
~~f~~e. Patient has received any of the following concomitant medications ~~for dystonia and chorea~~ within the specified exclusionary windows ~~of~~from screening or day 1 (whichever comes first) of this study: ~~– within 3 months: depot neuroleptics~~ – within 30 days: tetrabenazine or valbenazine – within 21 days: reserpine – within 14 days: ~~neuroleptics (oral), typical and atypical antipsychotics, metoclopramide,~~ levodopa, dopamine agonists, and monoamine oxidase inhibitors	e. Patient has received any of the following concomitant medications within the specified exclusionary windows from screening or day 1 (whichever comes first) of this study: – within 30 days: tetrabenazine or valbenazine – within 21 days: reserpine – within 14 days: levodopa, dopamine agonists, and monoamine oxidase inhibitors	Clarification of the concomitant medication types and criteria for patient exclusion
~~g~~f. Patient has received treatment with stem cells, deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation for treatment of abnormal movements or CP since the week 15 visit of Study TV50717-CNS-30080, or the patient is not in a stable clinical condition.	f. Patient has received treatment with stem cells, deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation for treatment of abnormal movements or CP since the week 15 visit of Study TV50717-CNS-30080, or the patient is not in a stable clinical condition.	Clarification
~~h~~g. Patient had a~~s recent~~ surgical procedure since the week 15 visit of Study TV50717-CNS-30080 or is anticipated to have a surgical procedure during the study that, in the	g. Patient had a surgical procedure since the week 15 visit of Study TV50717-CNS-30080 or is anticipated to have a surgical procedure during the study that, in the opinion of	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
opinion of the investigator, makes the patient unsuitable for the study.	the investigator, makes the patient unsuitable for the study.	
~~j~~i. Patient has a QT interval corrected for heart rate (QTc) using Fridericia's formula (QTcF) value >450 msec on 12-lead ECG at screening or day 1 (whichever comes first) of this study.	i. Patient has a QT interval corrected for heart rate (QTc) using Fridericia's formula (QTcF) value >450 msec on 12-lead ECG at screening or day 1 (whichever comes first) of this study .	Clarification
~~l~~k. Patient has evidence of hepatic impairment, as indicated by the following: – aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5× the upper limit of the normal range (ULN) at ~~day 1~~the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable – alkaline phosphatase (ALP) or total bilirubin (Tbil) >2×ULN at ~~day 1~~ the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable Note: Patients with abnormalities in 2 or more of AST, ALT, ALP, and Tbil ~~the following clinical laboratory~~ parameters that do not meet the above laboratory criteria for exclusion based on hepatic impairment must be approved for enrollment by the medical monitor~~: AST, ALT, ALP, and Tbil~~.	k. Patient has evidence of hepatic impairment, as indicated by the following: – aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5× the upper limit of the normal range (ULN) at the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable – alkaline phosphatase (ALP) or total bilirubin (Tbil) >2×ULN at the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable Note: Patients with abnormalities in 2 or more of AST, ALT, ALP, and Tbil parameters that do not meet the above laboratory criteria for exclusion based on hepatic impairment must be approved for enrollment by the medical monitor.	Clarification
~~m~~l. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5×ULN at ~~day 1~~the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable	l. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5×ULN at the week 15 or week 16 visit of Study TV50717-CNS-30080 or screening of this study, as applicable	Clarification
~~o~~p. Patient has a history of or acknowledges alcohol or substance abuse~~, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V™)~~.	p. Patient has a history of or acknowledges alcohol or substance abuse.	Clarification
~~r~~q. Patient has a positive urine drug screen test result since the week 15 or week 16 visit of Study TV50717-CNS-30080 or at screening (as applicable) of this study (with exception of medications listed in ~~Table 10~~Table 11 of	q. Patient has a positive urine drug screen test result since the week 15 or week 16 visit of Study TV50717-CNS-30080 or at screening (as applicable) of this study (with exception of medications listed in Table 11 of Appendix	Clarification provided with regards to urine drug screen exclusion criteria 'r"

Protocol text with changes shown	New wording	Reason/Justification for change
Appendix H or a justified medical explanation). Any request to include a patient with a positive urine drug screen test result should be discussed with, and approved by, the medical monitor. ~~or is unable to refrain from substance abuse throughout the study~~.	H or a justified medical explanation). Any request to include a patient with a positive urine drug screen test result should be discussed with, and approved by, the medical monitor.	
4.3. Withdrawal Criteria and Procedures for the Patient (Other sections affected by these changes: 7.9)		
The investigator also has the right to withdraw a patient from the IMP in the event of intercurrent illness, adverse events, pregnancy (see Section 7.3), or change in concomitant treatment (see Appendix H); patient engages in alcohol or other substance abuse; patient or parent(s)/legally acceptable representative withdraws consent or requests discontinuation from the IMP; the sponsor requests withdrawal of the patient or other reasons concerning the health or well being of the patient; or other reasons concerning the health or well being of the patient, or in the event of lack of cooperation. If a post-~~day 1~~treatment QTcF value >500 msec or change from screening or day 1 >60 msec is found, the investigator should repeat the ECG assessment twice and then compare the last pre treatment QTcF value ~~(baseline)~~ to the average of the 3 post ~~day 1~~treatment QTcF values. TEV 50717 must be stopped for any confirmed post-~~day 1~~treatment QTcF average value >500 msec or average increase from screening or day 1 >60 msec. Patients experiencing an adverse event leading to discontinuation or any other adverse event at the discretion of the investigator of TEV-50717 should have a single blood sample collected as soon as possible after the adverse event and within 48 hours for the measurement of TEV-50717, α-HTBZ and β-HTBZ concentrations, if possible. To permit the assessment of 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.	The investigator also has the right to withdraw a patient from the IMP in the event of intercurrent illness, adverse events, pregnancy (see Section 7.3), or change in concomitant treatment (see Appendix H); patient engages in alcohol or other substance abuse; patient or parent(s)/legally acceptable representative withdraws consent or requests discontinuation from the IMP; the sponsor requests withdrawal of the patient or other reasons concerning the health or well being of the patient; or other reasons concerning the health or well being of the patient, or in the event of lack of cooperation. If a post-treatment QTcF value >500 msec or change from screening or day 1 >60 msec is found, the investigator should repeat the ECG assessment twice and then compare the last pre treatment QTcF value to the average of the 3 post treatment QTcF values. TEV 50717 must be stopped for any confirmed post-treatment QTcF average value >500 msec or average increase from screening or day 1 >60 msec. Patients experiencing an adverse event leading to discontinuation or any other adverse event at the discretion of the investigator of TEV-50717 should have a single blood sample collected as soon as possible after the adverse event and within 48 hours for the measurement of TEV-50717, α-HTBZ and β-HTBZ concentrations, if possible. To permit the assessment of 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.	Criteria for patient withdrawal was clarified and elaborated upon Additional guidance provided on how to handle blood samples for patients experiencing an adverse event leading to discontinuation

Protocol text with changes shown	New wording	Reason/Justification for change
4.5 Rescreening		
See New wording column	A patient who is screened but not enrolled (eg, because inclusion criteria were not met, exclusion criteria were met, or enrollment did not occur within the specified time) may be considered for rescreening 1 time if there is a change in the patient's medical background or other relevant change. (Note: the medical monitor should approve rescreening after review of the enabling reasons.) Patients may have individual parameters retested at the discretion of both the investigator and the sponsor. If the patient is rescreened, an informed consent form (ICF) will need to be re-signed.	Section added to provide clarification around rescreening procedures
5.1.1.2.Dose Modification and Dose Stratification		
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 (Table 6 and Table 7).	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 (Table 6 and Table 7).	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
TEV-50717 will be administered as follows: • TEV-50717 cannot be crushed or split but should be swallowed whole; the TEV 50717 tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. Patients may be offered the optional use of a Medi+Straw®, which is a commercially available straw that can assist patients to overcome their swallowing difficulties. • Dosing and titration will be based on body weight at the day 1 visit and CYP2D6 impairment status, as shown in ~~Table 5~~Table 6 and ~~Table 6~~Table 7, respectively. • ~~After week 1, d~~Dose increases may not occur more frequently than every 5 days, except for patients ≥40 kg. For patients ≥40 kg, the first dose increase may be performed in an interval less than 5 days, only once, on day 3. • 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. • 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. • During the titration period, the dose of TEV-50717 should be adjusted ~~weekly~~ according to ~~Table 5~~Table 6 to identify a dose level that optimally reduces dyskinesia (as determined by the investigator, as indicated by a reduction in the CGI-I) and is well tolerated. Footnote "a" was added to Table 6: [a] Dose increases may not occur more frequently than every 5 days, except for patients ≥40 kg. For patients ≥40 kg, the first dose increase may be performed in an interval less than 5 days, only once, on day 3.	TEV-50717 will be administered as follows: • TEV-50717 cannot be crushed or split but should be swallowed whole; the TEV 50717 tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. Patients may be offered the optional use of a Medi+Straw®, which is a commercially available straw that can assist patients to overcome their swallowing difficulties. • Dosing and titration will be based on body weight at the day 1 visit and CYP2D6 impairment status, as shown in Table 6 and Table 7, respectively. • Dose increases may not occur more frequently than every 5 days, except for patients ≥40 kg. For patients ≥40 kg, the first dose increase may be performed in an interval less than 5 days, only once, on day 3. • 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. • 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. • During the titration period, the dose of TEV-50717 should be adjusted according to Table 6 to identify a dose level that optimally reduces dyskinesia (as determined by the investigator, as indicated by a reduction in the CGI-I) and is well tolerated. Footnote "a" was added to Table 6: [a] Dose increases may not occur more frequently than every 5 days, except for patients ≥40 kg. For patients ≥40 kg, the first dose increase may be performed in an interval less than 5 days, only once, on day 3.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
Table 8: Investigational Medicinal Products Used in the Study		
Stored at controlled room temperature, 20°C-25°C (68°F-77°F)~~, protected from light and moisture~~	Stored at controlled room temperature, 20°C-25°C (68°F-77°F)	Study storage stipulations were clarified
5.2.1. Storage and Security		
TEV-50717 must be stored ~~protected from light,~~ at a controlled room temperature, 20ºC to 25ºC (68ºF to 77ºF), in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff.	TEV-50717 must be stored at a controlled room temperature, 20ºC to 25ºC (68ºF to 77ºF), in a dry, securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff.	Study drug storage stipulations were clarified
5.5. Restrictions		
As with other VMAT2 inhibitors (tetrabenazine and reserpine), patients should be advised that the concomitant use of alcohol or other sedating drugs with TEV-50717 may have additive effects and cause or worsen somnolence. ~~Given the age of the study population, the use of alcohol during this study is prohibited.~~	As with other VMAT2 inhibitors (tetrabenazine and reserpine), patients should be advised that the concomitant use of alcohol or other sedating drugs with TEV-50717 may have additive effects and cause or worsen somnolence.	Clarification
5.6. Prior and Concomitant Medication or Therapy		
At each clinic visit after screening or day 1 (whichever comes first), the investigator will ask patients and/or caregivers whether the patient has taken any new medications (other than TEV-50717) or has any change in current medications, including…	At each clinic visit after screening or day 1 (whichever comes first), the investigator will ask patients and/or caregivers whether the patient has taken any new medications (other than TEV-50717) or has any change in current medications, including	Clarification
Patients and/or caregivers will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered (other than TEV-50717) or there is any change in current medications, including over-the-counter medications.	Patients and/or caregivers will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered (other than TEV-50717) or there is any change in current medications, including over-the-counter medications.	Clarification
Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table ~~11~~12. ~~Prohibited antipsychotic drugs are listed in Appendix H, Table 12.~~	Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table 12.	Prohibited antipsychotic drugs table has been deleted

Protocol text with changes shown	New wording	Reason/Justification for change
5.7. Procedures for Monitoring Patient Compliance		
The investigator will be responsible for monitoring patient compliance. A check of compliance with TEV-50717 intake will be performed during each in-clinic visit and telephone contact ~~after TEV-50717 has been dispensed~~ and will be documented in each patient's file.~~; and~~ TEV-50717 accountability records will be completed during each in-clinic visit. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study. Poor compliance with study drug (ie, <80%) or overdose (ie, >105%) is to be recorded as an important deviation and expeditely reported to the medical monitor.	The investigator will be responsible for monitoring patient compliance. A check of compliance with TEV-50717 intake will be performed during each in-clinic visit and telephone contact and will be documented in each patient's file. TEV-50717 accountability records will be completed during each in-clinic visit. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study. Poor compliance with study drug (ie, <80%) or overdose (ie, >105%) is to be recorded as an important deviation and expeditely reported to the medical monitor.	Clarification
5.8. Temporary Discontinuation of Investigational Medicinal Product		
Dose adjustments of TEV 50717 (upward or downward) may be made during the ~~titration and~~ maintenance periods, 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 (Table 6 and Table 7). After the dose modification, the patients will remain at the modified dose ~~throughout that period~~ unless further dose adjustments are warranted, and will ~~otherwise~~ follow the visit schedule as outlined in the protocol.	Dose adjustments of TEV 50717 (upward or downward) may be made during the maintenance periods, 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 (Table 6 and Table 7). After the dose modification, the patients will remain at the modified dose unless further dose adjustments are warranted, and will follow the visit schedule as outlined in the protocol.	Clarification
Suspension of TEV-50717 treatment for up to 1 week, if warranted, is allowed. If a patient's serum potassium or magnesium falls below the lower limit of normal, TEV-50717 ~~must~~ should be suspended.	Suspension of TEV-50717 treatment for up to 1 week, if warranted, is allowed. If a patient's serum potassium or magnesium falls below the lower limit of normal, TEV-50717 should be suspended.	Clarification
Patients who restart TEV-50717 treatment will remain at the current dose unless further dose adjustments are warranted, and will ~~otherwise~~ follow the visit schedule as outlined in the protocol.	Patients who restart TEV-50717 treatment will remain at the current dose unless further dose adjustments are warranted, and will follow the visit schedule as outlined in the protocol.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
5.11. Total Blood Volume		
The total blood volume to be collected for each patient in this study is approximately 76~~72~~ mL.	The total blood volume to be collected for each patient in this study is approximately 76 mL.	Update to align with slightly increased blood draws as indicated in Appendix I
6. ASSESSMENT OF EFFICACY		
Efficacy in this study will be evaluated using MD-CRS part I total score, MD-CRS part II total score, CaGI-I, CGI-I, CGI-S, PEDI-CAT, UHDRS-TMS, UHDRS-TMC, UHDRS-TMD, and COPM. 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 all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly. At each study visit, as applicable, the investigator should compare the current scores to the baseline scores and any trends observed throughout the study.	Efficacy in this study will be evaluated using MD-CRS part I total score, MD-CRS part II total score, CaGI-I, CGI-I, CGI-S, PEDI-CAT, UHDRS-TMS, UHDRS-TMC, UHDRS-TMD, and COPM. 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 all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly. At each study visit, as applicable, the investigator should compare the current scores to the baseline scores and any trends observed throughout the study.	Clarification to provide recommendation to the sites regarding the order that each scale is administered
6.1.1. Movement Disorder-Childhood Rating Scale		
The MD-CRS will be ~~either carried over from the week 16 visit of Study TV50717-CNS-30080-W16 and~~ administered ~~by the investigational center physician~~ at the day 1 visit (Table 4) and at week 14, week 27, week 40, week 53/ET, and week 54/follow-up visits. The protocol refers to MD-CRS as a physician-rated scale, but in certain instances, based on the experience of the rater, certain non-physicians may be approved to rate the MD-CRS.	The MD-CRS will be administered at the day 1 visit (Table 4) and at week 14, week 27, week 40, week 53/ET, and week 54/follow-up visits (Table 5). The protocol refers to MD-CRS as a physician-rated scale, but in certain instances, based on the experience of the rater, certain non-physicians may be approved to rate the MD-CRS.	Clarifications provided on carry over and administration of the MD-CRS
6.1.2. Caregiver Global Impression of Improvement Scale		
The CaGI-I is to be ~~assessed~~ completed before all other investigator rated scales during visits where CaGI-I is collected (~~Table 4~~Table 5).	The CaGI-I is to be completed before all other investigator rated scales during visits where CaGI-I is collected (Table 5).	Clarification
6.1.4. Clinical Global Impression of Severity		

Protocol text with changes shown	New wording	Reason/Justification for change
The CGI-S is ~~carried over from Study TV50717-CNS-30080 W16~~ administered at the day 1 visit (Table 4) and …	The CGI-S is administered at the day 1 visit (Table 4) and …	Clarification
6.1.6. Unified Huntington's Disease Rating Scale-Total Motor Score		
See New wording column	The 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) (Huntington Study Group 1996). The 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) (Huntington Study Group 1996).	Revised to include the definitions of the UHDRS-TMC and the UHDRS-TMD
7.1.2. Recording and Reporting of Adverse Events		
For recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF ~~for this study~~ to the end of the follow up period.	For recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the follow up period.	
7.2. Safety Rating Scales		
Site-administered safety scales include the children's C-SSRS (Posner et al 2011), CBCL, ESRS (Chouinard and Margolese 2005), and ESS (Janssen et al 2017). 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 all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly. At each study visit, as applicable, the investigator should compare the current scores to the baseline scores and any trends observed throughout the study.	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 all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly. At each study visit, as applicable, the investigator should compare the current scores to the baseline scores and any trends observed throughout the study.	Text added to clarify that there is a recommended order of administration of scales that should be followed throughout the study's duration
7.2.1. Children's Columbia-Suicide Severity Rating Scale		

Protocol text with changes shown	New wording	Reason/Justification for change
The children's C-SSRS Since Last Visit is administered at screening and/or day 1, as applicable (Table 4), and at the weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up (Table 5). However, 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.	The children's C-SSRS Since Last Visit is administered at screening and/or day 1, as applicable (Table 4), and at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow up (Table 5). However, 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.	Clarification on C-SSRS administration and carry over expectations
A shift table for children's C SSRS categories at day 1 ~~(carried over from study TV50717-CNS-30080-W16)~~, compared to the worst (highest) category during the treatment period, will be presented.	A shift table for children's C SSRS categories at day 1, compared to the worst (highest) category during the treatment period, will be presented.	
7.2.2. Extrapyramidal Symptom Rating Scale		
The ESRS is ~~carried over from study TV50717-CNS-30080-W16 and~~ administered at the day 1 visit (Table 4) and at the weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits (Table 5).	The ESRS is administered at the day 1 visit (Table 4) and administered at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits (Table 5).	Clarification on ESRS administration and carry over expectations
7.2.3. Child Behavior Checklist (for Ages 6 to 18)		
The full CBCL assessment (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) will be completed at the day 1 visit (Table 4) and at the week 53/ET visit (Table 5). ~~The Competence part [Parts I to VII] will be carried over from study TV50717-CNS-30080-W15.~~ The Syndrome Scale part of the CBCL [behavioral items] will be ~~carried over from study TV50717-CNS-30080-W16 and~~ completed at weeks 3, 7, 14, 27, 40, and 54/follow-up visits (Table 5).	The full CBCL assessment (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) will be completed at the day 1 visit (Table 4) and at the week 53/ET visit (Table 5). The Syndrome Scale part of the CBCL [behavioral items] will be completed at weeks 3, 7, 14, 27, 40, and 54/follow-up visits (Table 5).	Text added to include and clarify expectations surrounding the administration of the CBCL
7.2.4. Epworth Sleepiness Scale (for Children and Adolescents)		
The ESS is ~~carried over from study TV50717-CNS-30080-W16 and~~ administered at the day 1 visit (Table 4) and at the weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits (Table	The ESS is administered at the day 1 visit (Table 4) and administered at weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits (Table 5).	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
5).		
7.3. Pregnancy		
All pregnancies of female patients participating in the study that occur since the week 15 visit of Study TV50717-CNS-30080, during ~~the s~~Study TV50717-CNS-30081, or within 14 days after the end of study are to be reported immediately once the investigator has become aware of the pregnancy. The pregnancy should be reported to…	All pregnancies of female patients participating in the study that occur since the week 15 visit of Study TV50717-CNS-30080, during Study TV50717-CNS-30081, or within 14 days after the end of study are to be reported immediately once the investigator has become aware of the pregnancy. The pregnancy should be reported to…	Clarification of pregnancy reporting process and timing
7.5.2.1. Beta-Human Chorionic Gonadotropin Tests		
See New wording column	For females who are postmenarchal or ≥12 years of age, the following β-HCG tests in urine or serum will be performed based on when the patient enrolls in the study: • If the patient enrolls between 1 and <2 weeks after the week 15 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, 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. • If the patient enrolls between 2 and ≤4 weeks after the week 15 visit of Study TV50717-CNS-30080 and does not have a clinically significant change, β-HCG tests in urine will be administered at day 1. • If the patient enrolls between 2 and ≤4 weeks after the week 15 visit of Study TV50717-CNS-30080 and has a clinically significant change OR enrolls more than 4 weeks and up to 6 months after the week 15 visit of Study TV50717-CNS-30080, β-HCG tests in serum will be administered at screening. A β-HCG test in urine will be performed at the day 1 visit. A patient with a positive β-HCG test in urine cannot be enrolled until a β-HCG test in serum has been performed	Text added to provide clarification around the assessment and timing of administration of β-HCG tests.

Protocol text with changes shown	New wording	Reason/Justification for change
	and is negative.	
During the treatment period, β-HCG tests in urine will be performed for females who are postmenarchal or ≥12 years of age ~~at day 1 and~~ at weeks 14, 27, 40, and 54/follow-up.	During the treatment period, β-HCG tests in urine will be performed for females who are postmenarchal or ≥12 years of age at weeks 14, 27, 40, and 54/follow-up.	Clarification
7.5.2.2. Urine Drug Screen		
…will preclude the patient from ~~randomization/~~enrollment or continued participation in the study. Some of the drugs listed in this urine drug screen may be permitted in certain cases when the particular medication is being used under a physician's or clinician's guidance and in compliance with the physician's/clinician's recommendation for a specific condition; for example, phenobarbital (barbiturates) for seizures, stimulant medications (including amphetamine, methylphenidate, and lisdexamfetamine) for attention deficit hyperactivity disorder, and opiates or oxycodone for pain, if the dosing has been stable for at least 4 weeks before screening or day 1 and if no changes to dose or frequency are anticipated during the course of the study. Such cases should be discussed with the medical monitor. For patients who are either using these medications or who have a positive drug screen for these substances or derivatives, such cases should be submitted to the medical monitor for consideration of participation in this study. If per the investigator's judgment, however, a patient does not meet the criteria for substance use disorder, a positive drug screen for these medications or derivatives, without medical explanation, should be discussed on a case-by-case basis with the medical monitor to determine the patient's eligibility, based on the information available.	…will preclude the patient from enrollment or continued participation in the study. Some of the drugs listed in this urine drug screen may be permitted in certain cases when the particular medication is being used under a physician's or clinician's guidance and in compliance with the physician's/clinician's recommendation for a specific condition; for example, phenobarbital (barbiturates) for seizures, stimulant medications (including amphetamine, methylphenidate, and lisdexamfetamine) for attention deficit hyperactivity disorder, and opiates or oxycodone for pain, if the dosing has been stable for at least 4 weeks before screening or day 1 and if no changes to dose or frequency are anticipated during the course of the study. Such cases should be discussed with the medical monitor. For patients who are either using these medications or who have a positive drug screen for these substances or derivatives, such cases should be submitted to the medical monitor for consideration of participation in this study. If per the investigator's judgment, however, a patient does not meet the criteria for substance use disorder, a positive drug screen for these medications or derivatives, without medical explanation, should be discussed on a case-by-case basis with the medical monitor to determine the patient's eligibility, based on the information available.	Clarification on the possible exceptions that may be considered upon conducting the urine drug screen
7.6. Vital Signs		
(The same position and arm/leg should be used each time vital signs are measured for a given patient.)	(The same position and arm/leg should be used each time vital signs are measured for a given patient.)	Clarification
7.9. Electrocardiography		
A 12 lead ECG will be recorded at the time points detailed in Table 4 and Table 5. All ECGs will be performed after at	A 12 lead ECG will be recorded at the time points detailed in Table 4 and Table 5. All ECGs will be performed after at	Text added to provide additional guidance to the investigator with

Protocol text with changes shown	New wording	Reason/Justification for change
least 5-minute rest in a supine or semi-supine position. The investigator should review the ECG at day 1 and at screening (in case a screening visit is performed) to determine patient eligibility for the study and subsequent ECGs for patient's continuation in the study.	least 5-minute rest in a supine or semi-supine position. The investigator should review the ECG at day 1 and at screening (in case a screening visit is performed) to determine patient eligibility for the study and subsequent ECGs for patient's continuation in the study.	regards to patient eligibility.
If a post-~~day 1~~treatment QTcF value >500 msec or change from screening or day 1 >60 msec is found, the investigator should repeat the ECG assessment twice and then compare the last pre treatment QTcF value ~~(baseline)~~ to the average of the 3 post ~~day 1~~treatment QTcF values. TEV 50717 must be stopped for any confirmed post-~~day 1~~treatment QTcF average value >500 msec or average increase from screening or day 1 >60 msec.	If a post-treatment QTcF value >500 msec or change from screening or day 1 >60 msec is found, the investigator should repeat the ECG assessment twice and then compare the last pre treatment QTcF value to the average of the 3 post treatment QTcF values. TEV-50717 must be stopped for any confirmed post-treatment QTcF average value >500 msec or average increase from screening or day 1 >60 msec.	Clarification
7.12. Concomitant Medication or Treatment		
Patients and/or caregivers will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered (other than TEV-50717) or there is any change in current medications, including over the counter medications.	Patients and/or caregivers will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered (other than TEV-50717) or has any change in current medications, including over the counter medications.	Revisions to concomitant medication stipulations Text added to provide additional clarity around patient considerations pertaining to concomitant medications and the responsibilities of the medical monitor
…under the guidance, supervision, or prescription of a clinician and anticipated to remain stable (dose and frequency) within the study duration.	…under the guidance, supervision, or prescription of a clinician and anticipated to remain stable (dose and frequency) within the study duration.	

Protocol text with changes shown	New wording	Reason/Justification for change
Patients who are either using cannabis or its derivatives or formulations or patients who have a positive drug screen for cannabis or its derivatives or formulations ~~can~~ must be submitted to the medical monitor for consideration of participation in this study. ~~Patients with a substance use disorder (by Diagnostic and Statistical Manual of Mental Disorders, 5th edition, criteria) are excluded from this clinical trial.~~ Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix H, Table 11. Certain considerations mentioned in the table require the review of the medical monitor. Changes to the allowed medications may be permitted in the context of this study if pre-approved by the medical monitor..	Patients who are either using cannabis or its derivatives or formulations or patients who have a positive drug screen for cannabis or its derivatives or formulations must be submitted to the medical monitor for consideration of participation in this study. Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix H, Table 11. Certain considerations mentioned in the table require the review of the medical monitor. Changes to the allowed medications may be permitted in the context of this study if pre-approved by the medical monitor.	
Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table 12~~, while prohibited antipsychotic drugs are listed in Appendix H, Table 13~~.	Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table 12.	Table 13 was deleted
9.7. Efficacy Analysis		
See New wording column	• UHDRS-TMC (physician rated) • UHDRS-TMD (physician rated)	Text added to include the two newly added secondary objectives
15. REFERENCES		
See New wording column	National Institute of Neurological Disordes and Stroke (NINDS). Cerebral Palsy: Hope Through Research. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Cerebral-Palsy-Hope-Through-Research Accessed 27 February 2020	New reference added in the Introduction

Protocol text with changes shown	New wording	Reason/Justification for change
APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
See New wording column	Bioanalytic Laboratory [redacted] Watson Pharma Pvt, Ltd. Seawoods Grand Central Tower 2, Level-11, Wing-E, Plot N0 R-1, Sector 40, Nerul, Navi Mumbai-400706 India Tel. No. [redacted]	Administrative change
See New wording column	Scales Raters Training And Qualification Bracket Global LLC 785 Arbor Way Blue Bell, PA, 19422 Tel : [redacted]	Administrative change
APPENDIX C. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
1. Procedures for Screening and Enrollment		
Informed consent/assent, depending on the ~~child's~~patient's age and condition~~, as appropriate,~~ 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. Informed consent/assent ~~should be obtained at day 1 of Study TV50717-CNS-30081 ; however, 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. 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 (Figure 2).	Informed consent/assent, depending 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. 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. 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 (Figure 2).	Study procedures and assessments have been updated for consistency with changes made to the protocol body, Table 4, and Table 5. This justification applies to all changes indicated within Appendix C.

Protocol text with changes shown	New wording	Reason/Justification for change
2. Procedures Before TEV-50717 Treatment		
2.1 Procedures for Patients Who Enroll Between 1 and <2 Weeks After Study TV50717-CNS-30080 Week 15 Visit		
~~For all patients, the week 16 visit from Study TV50717-CNS-30080 may be the day 1 visit for Study TV50717-CNS-30081. Day 1 assessments for Study TV50717-CNS-30081 that are identical to Study TV50717-CNS-30080 baseline/week 15/16 visit assessments, whichever is most current, will serve as day 1 baseline values in this study and do not need to be repeated, except for orthostatic pulse rate, blood pressure (BP), Pediatric Evaluation Disability Inventory-Computer-Adapted Test (PEDI-CAT), and Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) which need to be repeated at day 1.~~ **a. ~~Assessments~~Data carried over from Study TV50717-CNS-30080 - ~~Baseline~~Screening** ~~• Medical history and psychiatric history~~ • Demographics **b. Assessments carried over from Study TV50717-CNS-30080 - Week 15/16** • Week 16 (W16) vital signs (~~pulse, BP,~~ body temperature, and respiratory rate) ~~• W16 urine pregnancy (beta-human chorionic gonadotropin [β-HCG]) test (required for all females who are postmenarchal or ≥12 years of age)~~ … ~~• administer the following assessments:~~ ~~– W16 Movement Disorder-Childhood Rating Scale (MD-CRS) part I~~ ~~– W16 MD-CRS part II~~ ~~– W16 Clinical Global Impression of Severity (CGI-S)~~ ~~– W16 Columbia-Suicide Severity Rating Scale (C-SSRS) ….~~	**a. Data carried over from Study TV50717-CNS-30080 - Screening** • Demographics **b. Assessments carried over from Study TV50717-CNS-30080 - Week 15/16** • Week 16 (W16) vital signs (body temperature, and respiratory rate) … **c. Day 1 Assessments** • medical history and psychiatric history • urine pregnancy (beta-human chorionic gonadotropin [β-HCG]) test (required for all females who are postmenarchal or ≥12 years of age) • administer the following assessments: – Movement Disorder-Childhood Rating Scale (MD-CRS) part I – MD-CRS part II – Clinical Global Impression of Severity (CGI-S) – Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI-CAT) – Child Behavior Checklist (CBCL) (for ages 6-18) (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) – Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) – Unified Huntington's Disease Rating Scale-Total Maximal Chorea (UHDRS-TMC) – Unified Huntington's Disease Rating Scale-Total Maximal Dystonia (UHDRS-TMD) – Canadian Occupational Performance Measure	

Protocol text with changes shown	New wording	Reason/Justification for change
~~– W16 Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II~~ ~~– Child Behavior Checklist (for ages 6-18) (CBCL) (full assessment [Competence and Syndrome Scales]) (Competence part [Parts I to VII] week 15 and Syndrome Scale [behavioral items] week 16 data from Study TV50717-CNS-30080 will be used)~~ ~~– W16 Epworth Sleepiness Scale (ESS) (for children and adolescents)~~ **c. Day 1 Assessments** • medical history and psychiatric history • administer the following assessments: – Movement Disorder-Childhood Rating Scale (MD-CRS) part I – MD-CRS part II – Clinical Global Impression of Severity (CGI-S) – Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI CAT) – Child Behavior Checklist (CBCL) (for ages 6-18) (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) – Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) – Unified Huntington's Disease Rating Scale-Total Maximal Chorea (UHDRS-TMC) – Unified Huntington's Disease Rating Scale-Total Maximal Dystonia (UHDRS-TMD) – Canadian Occupational Performance Measure (COPM) – Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit (Note: 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	(COPM) – Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit (Note: 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.). If the patient turned 12 years old during or after Study TV50717-CNS-30080, but before screening or day 1 visit (whichever comes first) of Study TV50717-CNS-30081, the C-SSRS baseline/screening scale will be completed. – Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II – Epworth Sleepiness Scale (ESS) (for children and adolescents) • inquire about adverse events • review concomitant medications • dispense TEV-50717 • contact Interactive Web Response Systems (IWRS) 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. If all inclusion/exclusion criteria have been reviewed and are met, and the patient is eligible for treatment, he/she will be dispensed with study drug.	

Protocol text with changes shown	New wording	Reason/Justification for change
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.). If the patient turned 12 years old during or after Study TV50717-CNS-30080, but before screening or day 1 visit (whichever comes first) of Study TV50717-CNS-30081, the C-SSRS baseline/screening scale will be completed. – Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II – Epworth Sleepiness Scale (ESS) (for children and adolescents) • inquire about adverse events • review concomitant medications • dispense TEV-50717 • contact Interactive Web Response Systems (IWRS) 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. If all inclusion/exclusion criteria have been reviewed and are met, and the patient is eligible for treatment, he/she will be dispensed with study drug.		
2. Procedures Before TEV-50717 Treatment (Day 1)		
2.2 Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with no clinically significant changes since the week 15 visit of Study TV50717-CNS-30080		
See New wording column	Patients who enroll in the study between 2 and ≤4 weeks after the Study TV50717-CNS-30080 week 15 visit with no clinically significant changes since the week 15 visit of Study TV50717-CNS-30080 will undergo the following assessments: **a. Assessments carried over from Study TV50717-CNS-30080 - Week 15/16**	

Protocol text with changes shown	New wording	Reason/Justification for change
	• W15 or W16 (whichever is the most current) chemistry, hematology, urinalysis • W16 urine drug screen **b. Day 1 Assessments** • obtain informed consent/assent • review of eligibility criteria • medical history and psychiatric history • demographics • vital signs (pulse, BP, body temperature, and respiratory rate) • weight • physical examination • neurological examination • height • 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position) • urine pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age) • MD-CRS part I • MD-CRS part II • CGI-S • PEDI-CAT • UHDRS-TMS • UHDRS-TMC • UHDRS-TMD • COPM • C-SSRS Since Last Visit (Note: 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	

Protocol text with changes shown	New wording	Reason/Justification for change
	will only be presented to patients aged ≥12 years.) If the patient turned 12 years old during Study or after Study TV50717-CNS-30080, but before screening or day 1 visit (whichever comes first) of Study TV50717-CNS-30081, the C-SSRS baseline/screening scale will be completed. • ESRS subscales I and II • CBCL (for ages 6 to 18) (full assessment Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) • ESS (for children and adolescents) • inquire about adverse events • review concomitant medications • dispense TEV-50717 • contact IWRS If all inclusion/exclusion criteria have been reviewed and are met, and the patient is eligible for treatment, he/she will be dispensed with study drug. For patients who enroll in the study Between 2 and ≤4 Weeks after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.	

Protocol text with changes shown	New wording	Reason/Justification for change
2. Procedures Before TEV-50717 Treatment (Day 1)		
2.3 Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with Clinically Significant Changes and for Patients Who Enroll More Than 4 Weeks and up to 6 Months After Study TV50717-CNS-30080 Week 15 Visit		
See New wording column	The patient will undergo all screening procedures. Patients who remain eligible for participation in the study will be asked to return for day 1 assessments. **a. Screening** • obtain informed consent/assent • review of eligibility criteria • medical history and psychiatric history • demographics • vital signs (pulse, BP, body temperature, and respiratory rate) • weight • physical examination • neurological examination • height • 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position) • chemistry, hematology, urinalysis • urine drug screen • serum pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age) • C-SSRS Since Last Visit (Note: 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.) If the patient turned 12 years old during or after Study TV50717-CNS-30080, but before screening or day 1	

Protocol text with changes shown	New wording	Reason/Justification for change
	visit (whichever comes first) of Study TV50717-CNS-30081, the C-SSRS baseline/screening scale will be completed. • CBCL (for ages 6 to 18) (full assessment Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) • inquire about adverse events • review concomitant medications • contact IWRS **b. Day 1** • review of eligibility criteria • vital signs (pulse, BP, body temperature, and respiratory rate) • weight • physical examination • neurological examination • urine pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age) • MD-CRS part I • MD-CRS part II • CGI-S • PEDI-CAT • UHDRS-TMS • UHDRS-TMC • UHDRS-TMD • COPM • C-SSRS Since Last Visit (Note: 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	

Protocol text with changes shown	New wording	Reason/Justification for change
	will only be presented to patients aged ≥12 years.) If the patient turned 12 years old between screening and day 1, the C-SSRS baseline/screening scale will be completed. • ESRS subscales I and II • CBCL (for ages 6-18) Syndrome Scale (behavioral items) • ESS (for children and adolescents) • inquire about adverse events • review concomitant medications • dispense TEV-50717 • contact IWRS If all inclusion/exclusion criteria have been reviewed and are met, and the patient is eligible for treatment, he/she will be dispensed with study drug. For patients who enroll in the study more than 2 weeks and up to 6 months after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.	
3. Procedures During TEV-50717 Treatment		
a. Titration Period (Weeks 1 to 7)		
ii. In-clinic Visits (Weeks 3 and 7)		
• dispense/collect TEV-50717 (During the week 3 visit, the investigator (or designee) will make sure the patient receives the evening dose to complete the week3 dosing for that day. Refer to the pharmacy manual for further details). • collect used and unused TEV-50717 bottles (Note: At the week 3 in-clinic visit, accountability will be performed on all bottles returned except for patients who receive 1 bottle back to complete the week 3 in-clinic evening dose. Refer to the pharmacy manual for	• dispense/collect TEV-50717 (During the week 3 visit, the investigator (or designee) will make sure the patient receives the evening dose to complete the week3 dosing for that day. Refer to the pharmacy manual for further details). • collect used and unused TEV-50717 bottles (Note: At the week 3 in-clinic visit, accountability will be performed on all bottles returned except for patients who receive 1 bottle back to complete the week 3 in-clinic evening dose.	

Protocol text with changes shown	New wording	Reason/Justification for change
further details.) • assess drug accountability/compliance/supply (Note: At the week 3 in-clinic visit, accountability will be performed on all bottles returned except for patients who receive 1 bottle back to complete the week 3 in-clinic evening dose. Refer to the pharmacy manual for further details.) • contact IWRS	Refer to the pharmacy manual for further details.) • assess drug accountability/compliance/supply (Note: At the week 3 in-clinic visit, accountability will be performed on all bottles returned except for patients who receive 1 bottle back to complete the week 3 in-clinic evening dose. Refer to the pharmacy manual for further details.) • contact IWRS	
b. Maintenance Period (Weeks 14 to 53/Early Termination)		
i. In-clinic Visits (Weeks 14, 27, 40, and 53/Early Termination)		
See New wording column	– UHDRS-TMC – UHDRS-TMD – contact IWRS	
4. Procedures After TEV-50717 Treatment (Follow-Up)		
b. Telephone Contact (Week 55)		
Patients who participate in the study in compliance with the protocol for at least 534 weeks of treatment will be considered to have completed the ~~study~~treatment. See Section 5.4 for the definition of the end of study.	Patients who participate in the study in compliance with the protocol for at least 53 weeks of treatment will be considered to have completed the treatment. See Section 5.4 for the definition of the end of study.	
5. Unscheduled Visits		
The following procedures/assessments will be performed at all in-clinic unscheduled visits: • contact IWRS	The following procedures/assessments will be performed at all in-clinic unscheduled visits: • contact IWRS	

Protocol text with changes shown	New wording	Reason/Justification for change
APPENDIX H. LIST OF ALLOWED AND PROHIBITED MEDICATIONS		
Table 11: Allowed Medications		
See New wording column	Table 11 has been revised as described below: • Added text to include dose was "anticipated to remain stable (dose and frequency) within the study duration" • Included additional allowed medications • Provided clarification around permissible use/receipt of botulinum neurotoxin (BoNT) with approval from the medical monitor. • Added a table note that changes to any dose required pre-approval from medical monitor	Table 11 has been revised to clarify the updated expectations surrounding allowed medications in alignment with recent updates to the protocol body and inclusion/exclusion criteria
Table 12: Prohibited Antipsychotic Drugs		
Table deleted		Table 12 deleted
APPENDIX I. TOTAL BLOOD VOLUME		
Total blood volume to be collected for each patient in this study is approximately ~~72~~76 mL. *See New wording column*	Total blood volume to be collected for each patient in this study is approximately 76 mL. The Total Blood Volumes tables has been revised as described below: • Added screening as part of the baseline column • Added collection of blood for β-HCG at baseline (day 1) • Added collection of blood for TEV-50717 concentration at Week 53/ET and unscheduled timepoints • Updated list of abbreviations	Total blood volume/draw amount has been updated to 76 mL. Total blood volume table has been revised to account for an additional ~4 mL of blood as per the changes implemented in this amendment

Protocol text with changes shown	New wording	Reason/Justification for change
c Serum β-HCG to be ~~taken only~~performed at screening for patients who enroll between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit and had a clinically significant change and for patients who enroll >4 weeks and up to 6 months after Study TV50717-CNS-30080 week 15 visit and at week 53 for all patients.	c Serum β-HCG to be performed at screening for patients who enroll between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit and had a clinically significant change and for patients who enroll >4 weeks and up to 6 months after Study TV50717-CNS-30080 week 15 visit and at week 53 for all patients.	Footnote revised for clarity
See New wording column	d Patients experiencing an adverse event leading to discontinuation or any other adverse event at the discretion of the investigator of TEV-50717 should have a single blood sample collected as soon as possible after the adverse event and within 48 hours for the measurement of TEV-50717, and α- and β-HTBZ concentrations, if possible. To permit the assessment of 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.	Footnote added for alignment with changes made to protocol body. Additional guidance provided to the investigator regarding how to handle patients who experience adverse events leading to discontinuation

16.8. Amendment 01 Dated 02 October 2019

The primary reason for this amendment is to provide clarification for the day 1 procedures in Study TV50717-CNS-30081 relative to the same assessments performed at weeks 15 and 16 in the parent Study TV50717-CNS-30080.

This amendment is considered to be substantial by the sponsor's authorized representative. These substantive changes included revised inclusion and exclusion criteria and new criteria for early withdrawal of study treatment.

Other minor or editorial non-substantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

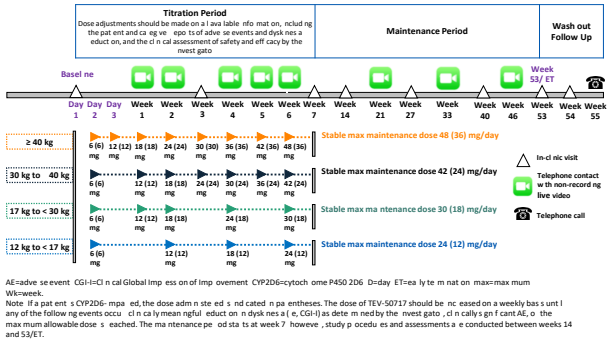
All of the changes in the first table below reflect what has changed from the original protocol. All of the changes in the second table below reflect what has changed from the Letter of Clarification 01 (Section 16.10).

Protocol text with changes shown	New wording	Reason/Justification for change
Title Page (Other sections affected by these changes: Investigator Agreement, Synopsis)		
EUDRACT Number: ~~NA~~2019-001807-19	**EudraCT Number:** 2019-001807-19	
Synopsis and Throughout the protocol		
parent/caregiver	caregiver	
caregiver/adult	caregiver	
caregiver/parent	caregiver	
Synopsis [Planned Study Period]		
Q~~4~~2 2019 to Q~~4~~1 2022	Q4 2019 to Q4 2022	Clarification
Synopsis [General Study Design] (Other sections affected by these changes: Brief Summary of Study Design for the Trial Registry(s) and 3.1)		
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 1 week following the week 16 visit.	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 1 week following the week 16 visit.	Clarification
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).	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).	Clarification
Synopsis [General Study Design] (Other sections affected by these changes: 3.1)		
For the purposes of this protocol, a caregiver is defined as an adult, who is familiar with the patient and responsible for daily care, enabling that person to effectively complete the protocol requirements. The caregiver accompanies the patient to the visits and provides input to the relevant scales as required by the protocol. For patients who are minors, the caregiver is typically a parent or legal guardian. In some countries, an adult (such as grandparent or nurse) can be appointed by the parent or legal guardian (as per local regulations and laws) and would take over this responsible as caregiver. The parent or legal guardian only has to sign the parent/legal guardian ICF and not the caregiver ICF. For adult patients, a caregiver must be appointed by the	For the purposes of this protocol, a caregiver is defined as an adult, who is familiar with the patient and responsible for daily care, enabling that person to effectively complete the protocol requirements. The caregiver accompanies the patient to the visits and provides input to the relevant scales as required by the protocol. For patients who are minors, the caregiver is typically a parent or legal guardian. In some countries, an adult (such as grandparent or nurse) can be appointed by the parent or legal guardian (as per local regulations and laws) and would take over this responsible as caregiver. The parent or legal guardian only has to sign the parent/legal guardian ICF and not the caregiver ICF. For adult patients, a caregiver must be appointed by the	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
patient; this can be the parent or other adult as appropriate and according to local laws and regulations. For patients who are minors, certain responsibilities in the protocol can only be completed by the parent/legal guardian, ie, informed consent, withdrawal of consent, requests for discontinuation of IMP, or withdrawal from the study for any reason. To further clarify, the caregiver is not allowed to make decisions on the child's health, or where "parent/legal guardian" is specifically indicated in the protocol.	patient; this can be the parent or other adult as appropriate and according to local laws and regulations. For patients who are minors, certain responsibilities in the protocol can only be completed by the parent/legal guardian, ie, informed consent, withdrawal of consent, requests for discontinuation of IMP, or withdrawal from the study for any reason. To further clarify, the caregiver is not allowed to make decisions on the child's health, or where "parent/legal guardian" is specifically indicated in the protocol.	
Synopsis [Brief Summary of Study Design for the Trial Registry(s)]		
~~For p~~Patients can roll~~ing~~ over from Study TV50717-CNS-30080~~,~~ on the same days as the week 16 visit, or within 1 week from the week 16 visit, and that will be the day 1 visit for Study TV50717-CNS-30081. ~~If the patient does not wish to participate in Study TV50717-CNS-30081 at that visit, the patient can enroll up to 1 week following the week 16 visit.~~ The end of study is defined as the date of the week 55 follow-up telephone contact of the last participant.	Patients can roll over from Study TV50717-CNS-30080 on the same day as the week 16 visit or within 1 week from the week 16 visit, and that will be their day 1 visit for Study TV50717-CNS-30081. The end of study is defined as the date of the week 55 follow-up telephone contact of the last participant.	Clarification
Synopsis [Brief Summary of Study Design for the Trial Registry(s)] (Other sections affected by these changes: 3.2)		
The study is expected to start by the end of Q4~~2~~ 2019 and to last until ~~early~~ Q4 2022.	The study is expected to start by the end of Q4 2019 and to last until Q4 2022.	Clarification
Synopsis [Investigational Medicinal Products] (Other sections affected by these changes: 1.1.1, 5.1.1, 5.1.1.1, and Table 8)		
TEV-50717 oral tablets (test IMP) are ~~available in commercially available the following dose strengths:~~ 6, 9, and 12 mg dose strengths. ~~15, and 18 mg~~. Each dose strength will have a marking ~~of SD 6, SD 9, SD 12, SD 15, and SD 18~~ corresponding to the dose strength on the label. ~~It is possible that all dose strengths may not be used during the study.~~ TEV-50717 will be supplied as ~~20 or~~ 60-count ~~white~~ tablets ~~per dose strength~~ per bottle. Each dose strength will be a colored tablet with a marking of "SD" and the corresponding strength.	TEV-50717 oral tablets (test IMP) are 6, 9, and 12 mg dose strengths. Each dose strength will have a marking corresponding to the dose strength on the label. TEV-50717 will supplied in 60-count tablets per bottle. Each dose strength will be a colored tablet with a marking of "SD" and the corresponding strength.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
Synopsis [Duration of Patient Participation and Maximal Exposure to IMP]		
Any patient that ~~turns 18 years of age~~ reaches the age of legal competence to give informed consent during the course of Study TV50717-CNS-30081 will need to be re-consented as an adult. When the patient is a minor advancing to the next age range (new assent available and patient is still considered a minor by local law), the patient may need to sign on new assent appropriate for that age in order to continue participation in the study (in accordance to local laws and regulations).	Any patient that reaches the age of legal competence to give informed consent during the course of Study TV50717-CNS-30081 will need to be re-consented as an adult. When the patient is a minor advancing to the next age range (new assent available and patient is still considered a minor by local law), the patient may need to sign on new assent appropriate for that age in order to continue participation in the study (in accordance to local laws and regulations).	Clarification
Synopsis [Inclusion Criteria] (Other sections affected by these changes: 4.1)		
a. Patient ~~is of an eligible age from~~ has completed parent Study TV50717-CNS-30080. g. ~~Patient and caregiver/parent provide written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.~~For a patient who is a minor, the parent(s)/legal guardian(s) provides written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients (in accordance with local regulations) provide their own written informed consent. h. A caregiver will provide written informed consent after being assigned the role by an adult patient o, if this role is delegated by the parent/legal guardian of a patient who is a minor.	a. Patient has completed parent Study TV50717-CNS-30080. g. For a patient who is a minor, the parent(s)/legal guardian(s) provides written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients (in accordance with local regulations) provide their own written informed consent. h. A caregiver will provide written informed consent after being assigned the role by an adult patient or if this role is delegated by the parent/legal guardian of a patient who is a minor.	Clarification
Synopsis [Exclusion Criteria] (Other sections affected by these changes: 4.2)		
~~a. Patient has a predominant movement disorder other than dyskinesia.~~ ~~b. Patient's predominant motor symptoms are dystonic.~~ ~~c. Patient's predominant motor symptoms are spastic.~~ ~~d. Patient has another movement disorder that could impair the motor assessment in the MD-CRS part II.~~ a~~e~~. Patient has clinically significant depression at day 1 of	c. a. Patient has clinically significant depression at day 1 of this study.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
this study.		
d. ~~e~~i. Patient who is currently receiving or who has received botulinum neurotoxin (BoNT) in an investigational clinical trial. Note: Patients may be included in the study if they have at least 2 treatments of Food and Drug Administration-approved BoNT at a regular interval (eg, every 3 to 4 months), in reasonably stable dosages and locations (subject to investigator's judgment) to treat lower limb spasticity or dystonia. "Food and Drug Administration-approved BoNT" is to be defined as an FDA-approved compound, not necessarily an FDA-approved treatment for children. BoNT treatments other than FDA-approved drugs can be submitted to the medical monitor for consideration.	e. e. Patient who is currently receiving or who has received botulinum neurotoxin (BoNT) in an investigational clinical trial. Note: Patients may be included in the study if they have at least 2 treatments of Food and Drug Administration-approved BoNT at a regular interval (eg, every 3 to 4 months), in reasonably stable dosages and locations (subject to investigator's judgment) to treat lower limb spasticity or dystonia. "Food and Drug Administration-approved BoNT" is to be defined as an FDA-approved compound, not necessarily an FDA-approved treatment for children. BoNT treatments other than FDA-approved drugs can be submitted to the medical monitor for consideration.	Clarification
~~v~~r. Patient has a positive urine drug screen test result (with exception of medications listed in Table 10 of Appendix H) or is unable to refrain from substance abuse throughout the study.	r. Patient has a positive urine drug screen test result (with exception of medications listed in Table 10 of Appendix H) or is unable to refrain from substance abuse throughout the study.	
1.1.1. Background for TEV-50717 (Other sections affected by these changes: Table 7)		
TEV-50717 tablets are ~~available in the following dose strengths:~~ 6, 9, and 12~~, 15, and 18~~ mg, or other commercially available dose strengths, all of which are identical in size~~,~~ and shape~~, and color (white)~~. Each strength will be a colored tablet with a marking of "SD" and the corresponding strength. ~~It is possible that all dose strengths may not be used during the study.~~ The investigational medicinal product (IMP) will be supplied in ~~20 or~~ 60-count tablets ~~per dose strength~~ per bottle.	TEV-50717 tablets are 6, 9, and 12 mg, or other commercially available dose strengths, all of which are identical in size and shape. Each strength will be a colored tablet with a marking of "SD" and the corresponding strength. The investigational medicinal product (IMP) will be supplied in 60-count tablets per bottle.	Clarification
1.2.1.2. Nonclinical Pharmacokinetics and Drug Metabolism		
Tetrabenazine, α-HTBZ, and β-HTBZ and, by extension, their deuterated forms, do not inhibit or induce cytochrome P450 (CYP) isoenzymes at clinically relevant concentrations (Xenazine Prescribing Information 2017~~5~~).	Tetrabenazine, α-HTBZ, and β-HTBZ and, by extension, their deuterated forms, do not inhibit or induce cytochrome P450 (CYP) isoenzymes at clinically relevant concentrations (Xenazine Prescribing Information 2017).	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
1.2.2.1. Clinical Pharmacology Studies		
~~Seven~~Nine Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers.	Nine Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers.	Clarification
1.2.2. Clinical Studies		
The clinical development plan for TEV-50717 to date includes the following: • ~~seven~~ nine completed Phase 1 studies in healthy adult volunteers • ~~two ongoing Phase 1 studies in healthy adult volunteers~~	The clinical development plan for TEV-50717 to date includes the following: • nine completed Phase 1 studies in healthy adult volunteers	Clarification
Figure 1: Overall Study Schematic Diagram		
		Clarification
In the titration box: Dose adjustments should be made on all available information, including the patient and caregiver~~/adult~~ reports of adverse events and dyskinesia reduction, and the clinical assessment of safety and efficacy by the investigator *In the footnote:* The maintenance period starts at week ~~8~~7	*In the titration box*: Dose adjustments should be made on all available information, including the patient and caregiver reports of adverse events and dyskinesia reduction, and the clinical assessment of safety and efficacy by the investigator *In the footnote:* The maintenance period starts at week ~~8~~7	

Protocol text with changes shown	New wording	Reason/Justification for change
Table 4 Study Procedures and Assessments		
Row: Visit window (days) Column: BL ~~0 days~~	Row: Visit window (days) Column: BL	Clarification
Row: Informed consent/assent ~~and/or co-consent for patients 14 years of age and older~~	Row: Informed consent/assent	
Row: Evaluate/adjust TEV-50717 Column: Week 53/ET ~~X~~	Row: Evaluate/adjust TEV-50717 Column: Week 53/ET	
Row: Vital signs and weight Column: BL [X[l]]	Row: Vital signs and weight Column: BL [X[l]]	
Row: Urine drug screen Column: BL [X]	Row: Urine drug screen Column: BL [X]	
Row: β-HCG test Column: BL [X]	Row: β-HCG test Column: BL [X]	
Row: MD-CRS part I (physician rated) Column: BL [X]	Row: MD-CRS part I (physician rated) Column: BL [X]	
Row: MD-CRS part II (physician rated) Column: BL [X]	Row: MD-CRS part II (physician rated) Column: BL [X]	
Row: CGI-S (global, physician rated) Column: BL [X]	Row: CGI-S (global, physician rated) Column: BL [X]	

Protocol text with changes shown	New wording	Reason/Justification for change
Row: C-SSRS (children's since last visit) Column: BL [X]	Row: C-SSRS (children's since last visit) Column: BL [X]	
Row: ESRS (subscales I and II) Column: BL [X]	Row: ESRS (subscales I and II) Column: BL [X]	
Row: CBCL Column: BL [X]	Row: CBCL Column: BL [X]	
Row: ESS Column: BL [X]	Row: ESS Column: BL [X]	
Row: Assess TEV-50717 accountability/compliance/ supply[t] Column: 1	Row: Assess TEV-50717 accountability/compliance/ supply[t] Column: 1	
Row: Concomitant medications[t] Column: 1 Concomitant medications[et]	Row: Concomitant medications[t] Column: 1 Row: Concomitant medications[f]	
[a] Assessments indicated in brackets by "[X]" are representative of data carried over from baseline or week 15/16 of parent Study TV50717-CNS-30080, whichever is the most current. Screening evaluations for this open-label study will be performed as part of the baseline visit.	[a] Assessments indicated in brackets by "[X]" are representative of data carried over from baseline or week 15/16 of parent Study TV50717-CNS-30080, whichever is the most current. Screening evaluations for this open-label study will be performed as part of the baseline visit.	Clarification
[d] For all patients, the week 16 visit from Study TV50717-CNS-30080 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 the week 16 visit of parent Study TV50717-CNS-30080 or for any other reason, the patient can enroll up to 1 week following the week 16 visit. Day 1 assessments in Study TV50717-CNS-30081 that are identical to Study TV50717-CNS-30080	[d] For all patients, the week 16 visit from Study TV50717-CNS-30080 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 the week 16 visit of parent Study TV50717-CNS-30080 or for any other reason, the patient can enroll up to 1 week following the week 16 visit. Day 1 assessments in Study TV50717-CNS-30081 that are identical to Study TV50717-	To clarify some of the day 1 procedures in Study TV50717-CNS-30081 relative to the same assessments performed at weeks 15 and 16 in the parent Study TV50717-CNS-30080

Protocol text with changes shown	New wording	Reason/Justification for change
baseline/week 15/16 visit assessments, whichever is the most current, **do not** need to be repeated, except for orthostatic pulse rate, BP, PEDI-CAT, and UHDRS-TMS, which need to be repeated at Day 1.	CNS-30080 week 15/16 visit assessments, whichever is the most current, **do not** need to be repeated, except for orthostatic pulse rate and blood pressure, which need to be repeated at Day 1.	
[e] 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 ~~53~~ 55 visit.	[e] 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.	Clarification
[l] 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 day 1.	[l] 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 day 1.	
[o] For females who are postmenarchal or ≥12 years of age, a urine pregnancy test will be administered at day 1 and at weeks 14, 27,~~and~~ 40, and 54 while a serum pregnancy test will be administered at week 53, and if clinically indicated.	[o] For females who are postmenarchal or ≥12 years of age, a urine pregnancy test will be administered at day 1 and at weeks 14, 27, 40, and 54 while a serum pregnancy test will be administered at week 53, and if clinically indicated.	Clarification
[t] Study drug accountability will be assessed during clinical visits only.	[t] Study drug accountability will be assessed during clinical visits only.	Clarification
Section 3.3. Justification for Study Design and Selection of Population		
The study population will include pediatric and adolescent patients (6 through 18 years of age) with DCP with predominant choreiform movement disorder, who have had non progressive CP symptoms since infancy (≤2 years of age), and have completed Study TV50717-CNS-30080. The diagnosis of DCP is based on the Surveillance of Cerebral Palsy in Europe criteria (Cans 2000). "Predominant" in this instance indicates that the choreiform movement disorder is the main cause of impairment or distress.	The study population will include pediatric and adolescent patients (6 through 18 years of age) with DCP with predominant choreiform movement disorder, who have had non progressive CP symptoms since infancy (≤2 years of age), and have completed Study TV50717-CNS-30080. The diagnosis of DCP is based on the Surveillance of Cerebral Palsy in Europe criteria (Cans 2000). "Predominant" in this instance indicates that the choreiform movement disorder is the main cause of impairment or distress.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
Section 4.3. Withdrawal Criteria and Procedures for the Patient		
Patients are to be discontinued from the study for the following situations: • Laboratory evidence of diminished hepatic function, defined as an AST or ALT >2.5×ULN and ALP or total bilirubin >2×ULN • Patient develops neuroleptic malignant syndrome.	Patients are to be discontinued from the study for the following situations: • Laboratory evidence of diminished hepatic function, defined as an AST or ALT >2.5×ULN and ALP or total bilirubin >2×ULN • Patient develops neuroleptic malignant syndrome.	Added per MHRA request
All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after their ET visit; evaluations will be as described for the week ~~54~~55 visit.	All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after their ET visit; evaluations will be as described for the week 55 visit.	Clarification
Section 5.1.1. Test Investigational Medicinal Product		
TEV 50717 is coated with a ~~white~~ polymer coating to aid in swallowing. TEV-50717 tablets have been manufactured according to current Good Manufacturing Practice (GMP) regulations. TEV-50717 tablets will be supplied as 6-, 9-, and 12- ~~15-, and 18~~-mg tablets, or other commercially available dose strengths, by bottle and labeled according to applicable regulatory guidelines. ~~It is possible that all dose strengths may not be used during the study.~~ Each bottle pack (~~20- or~~ 60-count tablets per dose strength ~~per bottle~~) will contain a sufficient supply of drug until the next specified visit/telephone contact, plus overage to account for potential delays in study visits.	TEV 50717 is coated with a ~~white~~ polymer coating to aid in swallowing. TEV-50717 tablets have been manufactured according to current Good Manufacturing Practice (GMP) regulations. TEV-50717 tablets will be supplied as 6-, 9-, and 12-mg tablets, or other commercially available dose strengths, by bottle and labeled according to applicable regulatory guidelines. Each bottle pack (60-count tablets per dose strength) will contain a sufficient supply of drug until the next specified visit/telephone contact, plus overage to account for potential delays in study visits.	Clarification
Table 7: Investigational Medicinal Products Used in the Study		
Row: ~~Dosing instructions~~Packaging Column: 1	Row: Packaging Column: 1	Typographical error correction
Row: ~~Packaging~~Manufacturer Column: 1	Row: Manufacturer Column: 1	
Row: ~~Manufacturer~~Storage conditions Column: 1	Row: Storage conditions Column: 1	

Protocol text with changes shown	New wording	Reason/Justification for change
Row: Manufacturer Anesta, LLC Wiley Post Way Salt Lake City, UT 84116 Column: 2	Row: Manufacturer Anesta, LLC Wiley Post Way Salt Lake City, UT 84116 Column: 2	New contractor
Section 5.4. Treatment after the End of the Study		
There are no plans to provide further treatment to patients upon completion of the study. An extension to the study may be considered on an annual basis.	There are no plans to provide further treatment to patients upon completion of the study. An extension to the study may be considered on an annual basis.	Clarification
Section 5.6. Prior and Concomitant Medication or Therapy		
At each clinic visit after day 1, the investigator will ask patients and/or ~~parent(s)/~~caregiver whether ~~they or~~ the patient~~, respectively,~~ has~~ve~~ taken any medications (other than TEV-50717), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit.	At each clinic visit after day 1, the investigator will ask patients and/or caregiver whether the patient has taken any medications (other than TEV-50717), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit.	Clarification
Table 9: Clinical Laboratory Tests		
Row: Magnesium Column: 1	Row: Magnesium Column: 1	Typographical error correction
Section 5.8. Temporary Discontinuation of Investigational Medicinal Product		
Suspension of TEV-50717 treatment for up to 1 week, if warranted, is allowed. If a patient's serum potassium or magnesium falls below the lower limit of normal, TEV-50717 must be suspended. Since TEV-50717 does not have any known effect on potassium and magnesium levels, the reference to potassium and magnesium is in the context of other factors related to any current underlying condition, such as severe diarrhea or intake of drugs that lower serum potassium and magnesium. The investigator will be responsible to manage the patient's condition per the site's standard of care and assess continuation of treatment. The medical monitor ~~must~~should be contacted to discuss the suspension and possible resumption of the IMP~~determine the~~	Suspension of TEV-50717 treatment for up to 1 week, if warranted, is allowed. If a patient's serum potassium or magnesium falls below the lower limit of normal, TEV-50717 must be suspended. Since TEV-50717 does not have any known effect on potassium and magnesium levels, the reference to potassium and magnesium is in the context of other factors related to any current underlying condition, such as severe diarrhea or intake of drugs that lower serum potassium and magnesium. The investigator will be responsible to manage the patient's condition per the site's standard of care and assess continuation of treatment. The medical monitor should be contacted to discuss the suspension and possible resumption of the IMP.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
~~appropriate investigation and treatment~~. TEV-50717 treatment may only be restarted once serum potassium and/or magnesium levels have normalized.	TEV-50717 treatment may only be restarted once serum potassium and/or magnesium levels have normalized.	
Section 6.1.1. Movement Disorder-Childhood Rating Scale		
MD-CRS part II evaluates the severity of the movement disorder in a scale of 0 to 4 in 7 body regions, all areas in which dyskinesia can be seen in patients with CP. 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. The 7 body regions are (i) eye and periorbital region, (ii) face, (iii) tongue and perioral region, (iv) neck, (v) trunk, (vi) upper limb, and (vii) lower limb. The MD-CRS part II does not differentiate whether the dyskinesia is of the dystonic or choreiform phenotype, and the worst dyskinesia in any of the regions observed during the assessment session will be taken as the score for each affected body region. The minimum score is 0 (absent) and the maximum score is 28 (marked/prolonged). Assessment of MD-CRS part II items will be based solely on chorea in this study.	MD-CRS part II evaluates the severity of the movement disorder in a scale of 0 to 4 in 7 body regions, all areas in which dyskinesia can be seen in patients with CP. 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. The 7 body regions are (i) eye and periorbital region, (ii) face, (iii) tongue and perioral region, (iv) neck, (v) trunk, (vi) upper limb, and (vii) lower limb. The MD-CRS part II does not differentiate whether the dyskinesia is of the dystonic or choreiform phenotype, and the worst dyskinesia in any of the regions observed during the assessment session will be taken as the score for each affected body region. The minimum score is 0 (absent) and the maximum score is 28 (marked/prolonged). Assessment of MD-CRS part II items will be based solely on chorea in this study.	Clarification
The MD-CRS will be carried over from study TV50717-CNS-30080 W16 and administered by the investigational center physician at ~~day 1,~~ week 14, week 27, week 40, week 53/ET, and week 54/follow-up visits.	The MD-CRS will be carried over from study TV50717-CNS-30080 W16 and administered by the investigational center physician at week 14, week 27, week 40, week 53/ET, and week 54/follow-up visits.	Clarification
Section 6.1.4. Clinical Global Impression of Severity		
The CGI-S ~~carried over from study TV50717-CNS-30080 W16 and~~ administered at the day 1 visit (Table 4) and administered at week 14, week 27, week 40, week 53/ET, and week 54/follow up visits.	The CGI-S administered at the day 1 visit (Table 4) and administered at week 14, week 27, week 40, week 53/ET, and week 54/follow up visits.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
Section 7.2.1. Children's Columbia-Suicide Severity Rating Scale		
The children's C-SSRS assesses suicidal ideation and behaviors for all patients aged ≥12years to determine suicide risk. The children's C-SSRS Since Last Visit is carried over from study TV50717-CNS-30080 W16 and administered ~~at day 1, and~~ at the weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up. 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 assesses suicidal ideation and behaviors for all patients aged ≥12years to determine suicide risk. The children's C-SSRS Since Last Visit is carried over from study TV50717-CNS-30080 W16 and administered at the weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up. 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.	Clarification
The frequency and severity of suicidal ideation or behavior according to the children's C-SSRS questionnaire will be presented by visit and by treatment group. A shift table for children's C-SSRS categories at day 1 (carried over from study TV50717-CNS-30080 W16), compared to the worst (highest) category during the treatment period, will be presented.	The frequency and severity of suicidal ideation or behavior according to the children's C-SSRS questionnaire will be presented by visit and by treatment group. A shift table for children's C-SSRS categories at day 1 (carried over from study TV50717-CNS-30080 W16), compared to the worst (highest) category during the treatment period, will be presented.	Clarification
Section 7.2.2. Extrapyramidal Symptom Rating Scale		
The ESRS is carried over from study TV50717-CNS-30080 W16 and administered ~~at day 1, and~~ at the weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits.	The ESRS is carried over from study TV50717-CNS-30080 W16 and administered at the weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits.	Clarification
Section 7.2.3. Child Behavior Checklist (for Ages 6 to 18)		
The full CBCL assessment (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) will be completed ~~at day 1, and~~ at the week 53/ET visit. The Competence part [Parts I to VII] will be carried over from study TV50717-CNS-30080 W15. The Syndrome Scale part of the CBCL [behavioral items] will be carried over from study TV50717-CNS-30080 W16 and completed ~~at day 1, and~~ at weeks 3, 7, 14, 27, 40, ~~53/ET visit,~~ and 54/follow-up visits.	The full CBCL assessment (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items]) will be completed at the week 53/ET visit. The Competence part [Parts I to VII] will be carried over from study TV50717-CNS-30080 W15. The Syndrome Scale part of the CBCL [behavioral items] will be carried over from study TV50717-CNS-30080 W16 and completed at weeks 3, 7, 14, 27, 40, and 54/follow-up visits.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
Section 7.2.4. Epworth Sleepiness Scale (for Children and Adolescents)		
The ESS is carried over from study TV50717-CNS-30080 W16 and administered ~~at day 1, and~~ at the weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits.	The ESS is carried over from study TV50717-CNS-30080 W16 and administered at the weeks 3, 7, 14, 27, 40, 53/ET, and 54/follow-up visits.	Clarification
Section 7.5.2.1. Beta-Human Chorionic Gonadotropin Tests		
β-HCG tests in urine will be performed for females who are postmenarchal or ≥12 years of age at day 1 and at weeks 14, 27, ~~and~~ 40, and 54. β-HCG tests in serum will be performed for all female patients who are postmenarchal or ≥12 years of age ~~aged 12 years or older of childbearing potential~~ at week 53/ET and if clinically indicated.	β-HCG tests in urine will be performed for females who are postmenarchal or ≥12 years of age at day 1 and at weeks 14, 27, 40, and 54. β-HCG tests in serum will be performed for all female patients who are postmenarchal or ≥12 years of age at week 53/ET and if clinically indicated.	Corrected an omission and clarification
Section 7.10. Assessment of Suicidality		
~~Families and c~~Caregivers of patients being treated with TEV-50717 should be instructed to monitor patients for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.	Caregivers of patients being treated with TEV-50717 should be instructed to monitor patients for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.	Clarification
Section 7.11. Assessment of Depression		
~~Families and c~~Caregivers of patients are instructed to monitor the patients for any changes in or new onset of depressive symptoms and unusual changes in mood, cognition, or behavior, and to report such symptoms immediately to the investigator.	Caregivers of patients are instructed to monitor the patients for any changes in or new onset of depressive symptoms and unusual changes in mood, cognition, or behavior, and to report such symptoms immediately to the investigator.	Clarification
Section 7.12. Concomitant Medication or Treatment		
Concomitant therapy or medication usage will be monitored throughout the study according to time points detailed in Table 3. Parents/patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered, including over-the-counter medications. Any prescribed/administered medication should be reviewed with the investigator. ~~Of note, any formulation/derivative of cannabis is prohibited during the study.~~	Concomitant therapy or medication usage will be monitored throughout the study according to time points detailed in Table 3. Parents/patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed/administered, including over-the-counter medications. Any prescribed/administered medication should be reviewed with the investigator. Patients may be included in this study if they are using cannabis or formulations or derivatives of cannabis in	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
Patients may be included in this study if they are using cannabis or formulations or derivatives of cannabis in relatively stable amounts, for medical purposes (where applicable according to local regulation), under the guidance, supervision, or prescription of a clinician. Patients who are either using cannabis or its derivatives or formulations or patients who have a positive drug screen for cannabis or its derivatives or formulations can be submitted to the medical monitor for consideration of participation in this study. Patients with a substance use disorder (by Diagnostic and Statistical Manual of Mental Disorders, 5th edition, criteria) are excluded from this clinical trial. If per the investigator's judgment, however, a patient does not meet the criteria for substance use disorder, a positive drug screen for cannabis or its metabolites, without medical explanation, will be discussed on a case-by-case basis between the research site, the Medical Monitor, and the sponsor to determine the patient's eligibility, based on the information available. Patients should be advised that the recreational use of cannabis or its derivatives or formulations should be avoided during this study. The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP2D6 inhibitor. Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table 10, while prohibited antipsychotic drugs are listed in Appendix H, Table 11.	relatively stable amounts, for medical purposes (where applicable according to local regulation), under the guidance, supervision, or prescription of a clinician. Patients who are either using cannabis or its derivatives or formulations or patients who have a positive drug screen for cannabis or its derivatives or formulations can be submitted to the medical monitor for consideration of participation in this study. Patients with a substance use disorder (by Diagnostic and Statistical Manual of Mental Disorders, 5th edition, criteria) are excluded from this clinical trial. If per the investigator's judgment, however, a patient does not meet the criteria for substance use disorder, a positive drug screen for cannabis or its metabolites, without medical explanation, will be discussed on a case-by-case basis between the research site, the Medical Monitor, and the sponsor to determine the patient's eligibility, based on the information available. Patients should be advised that the recreational use of cannabis or its derivatives or formulations should be avoided during this study. The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QTc prolongation or that is a known strong CYP2D6 inhibitor. Prohibited medications that are associated with QTc prolongation are listed in Appendix H, Table 10, while prohibited antipsychotic drugs are listed in Appendix H, Table 11.	
Section 15. References		
Xenazine: Highlights of Prescribing Information. 2017~~5~~. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2017~~5~~/021894s013~~0~~lbl.pdf. Accessed 27 Oct 2015.	Xenazine: Highlights of Prescribing Information. 2017. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021894s013lbl.pdf. Accessed 16 Jul 2019.	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
Appendix A		
Sponsor's Authorized Representative: [redacted] Teva Pharmaceutical Industries, [redacted] [redacted] Cell: [redacted] [redacted]	**Sponsor's Authorized Representative:** [redacted] Teva Pharmaceutical Industries, [redacted] [redacted] Cell: [redacted] [redacted]	Change in Sponsor's representative
Appendix C, 2. Procedures Before TEV-50717 Treatment (Day 1)		
– Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II (week 16 data from Study TV50717-CNS-30080 will be used) – Child Behavior Checklist (for ages 6-18) (CBCL) (full assessment [Competence and Syndrome Scales]) (Competence part [Parts I to VII] week 15 and Syndrome Scale [behavioral items] week 16 data from Study TV50717-CNS-30080 will be used) – Epworth Sleepiness Scale (ESS) (for children and adolescents) (week 16 data from Study TV50717-CNS-30080 will be used)	– Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II (week 16 data from Study TV50717-CNS-30080 will be used) – Child Behavior Checklist (for ages 6-18) (CBCL) (full assessment [Competence and Syndrome Scales]) (Competence part [Parts I to VII] week 15 and Syndrome Scale [behavioral items] week 16 data from Study TV50717-CNS-30080 will be used) – Epworth Sleepiness Scale (ESS) (for children and adolescents) (week 16 data from Study TV50717-CNS-30080 will be used)	Clarification
Appendix C		
c. Day 1 Assessments<br~~The following procedures will be performed at the day 1 visit:~~ • obtain informed consent/assent ~~(or co-consent for patients 14 years of age and older where applicable)~~ • review of eligibility criteria ~~(required for all patients)~~ • ~~measure vital signs (pulse, blood pressure [BP], body temperature, and respiratory rate);~~ orthostatic BP and pulse should be measured after standing for at least 3 minutes (for patients who are able to stand) • ~~measure weight (Note: Weight must be measured with~~	**c. Day 1 Assessments** • obtain informed consent/assent • review of eligibility criteria • orthostatic BP and pulse should be measured after standing for at least 3 minutes (for patients who are able to stand) • perform 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position • administer the following assessments: - Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI CAT)	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
~~shoes and outerwear off.)~~ • perform 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position ~~[required for all patients])~~ ~~• perform urine drug screen~~ ~~• perform a urine pregnancy (beta-human chorionic gonadotropin [β-HCG]) test (required for all females who are postmenarchal or ≥12 years of age)~~ • administer the following assessments: ~~- Movement Disorder Childhood Rating Scale (MD-CRS) part I (week 16 data from Study TV50717-CNS-30080 will be used)~~ ~~- MD-CRS part II (week 16 data from Study TV50717-CNS-30080 will be used)~~ ~~- Clinical Global Impression of Severity (CGI-S) (week 16 data from Study TV50717-CNS-30080 will be used)~~ - Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI CAT) - Unified Huntington's Disease Rating Scale-Total ~~Maximal Chorea~~ Motor Score (UHDRS TMS) - Canadian Occupational Performance Measure (COPM) ~~- Columbia-Suicide Severity Rating Scale (C-SSRS) (Note: 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.)~~ ~~- Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II (week 16 data from Study TV50717-CNS-30080 will be used)~~	- Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS TMS) - Canadian Occupational Performance Measure (COPM) • dispense TEV-50717 • inquire about adverse events • review concomitant medications	

Protocol text with changes shown	New wording	Reason/Justification for change
~~– Child Behavior Checklist (for ages 6-18) (CBCL) (full assessment [Competence and Syndrome Scales]) (Competence part [Parts I to VII] week 15 and Syndrome Scale [behavioral items] week 16 data from Study TV50717-CNS-30080 will be used)~~ ~~– Epworth Sleepiness Scale (ESS) (for children and adolescents) (week 16 data from Study TV50717-CNS-30080 will be used)~~ • dispense TEV-50717 • inquire about adverse events • review concomitant medications		
i In-clinic Visits (Weeks 14, 27, 40, and 53/Early Termination) • evaluate and, if required, adjust TEV-50717 dose <u>at weeks 14, 27, and 40</u>	**i In-clinic Visits (Weeks 14, 27, 40, and 53/Early Termination)** • evaluate and, if required, adjust TEV-50717 dose at weeks 14, 27, and 40	Clarification
Appendix D		
Any deviation from the protocol 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 deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to investigational medicinal product (IMP) administration; use of prohibited medications. ~~Important protocol deviations will be identified and recorded by investigational center personnel in the case report form (CRF).~~ All important protocol deviations will be reported to the responsible IEC/IRB, as required.	Any deviation from the protocol 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 deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to investigational medicinal product (IMP) administration; use of prohibited medications. All important protocol deviations will be reported to the responsible IEC/IRB, as required.	Clarification
Appendix F		
Females ~~(aged 12 years or older)~~ of childbearing potential are defined as the following:	Females of childbearing potential are defined as the following:	Clarification

Protocol text with changes shown	New wording	Reason/Justification for change
Table 10: Allowed Medications		
Column: Generic/Drug class Row: Cannabis or formulations or derivatives of cannabis	Column: Generic/Drug class Row: Cannabis or formulations or derivatives of cannabis	
Column: Condition Row: Patients may be included in this study if they are using cannabis or formulations or derivatives of cannabis in relatively stable amounts, for medical purposes (where applicable according to local regulation), under the guidance, supervision, or prescription of a clinician.	Column: Condition Row: Patients may be included in this study if they are using cannabis or formulations or derivatives of cannabis in relatively stable amounts, for medical purposes (where applicable according to local regulation), under the guidance, supervision, or prescription of a clinician.	

Letter of Clarification 01 text with changes shown	New wording	Reason/Justification for change
Synopsis [General Study Design] (Other sections affected by these changes: Brief Summary of Study Design for the Trial Registry(s), 3.1, and 16.3)		
For all patients, the week 16 visit from Study TV50717-CNS-30080 may be the day 1 visit for Study TV50717-CNS-30081. Day 1 assessments for Study TV50717-CNS-30081 that are identical to Study TV50717-CNS-30080 week 15/16 visit assessments, whichever is the most current, **do not** need to be repeated, except for orthostatic pulse rate and blood pressure, which need to be repeated at day 1. In addition, the following applies for day 1 baseline assessments for this study: • clinically significant laboratory abnormalities identified at week 15 in Study TV50717-CNS-30080 are to be repeated at week 16 of the parent study for eligibility of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. ~~These findings are only required to be shared with the medical monitor as required per the inclusion/exclusion criteria.~~ Any abnormalities which are listed in the inclusion/exclusion criteria must be discussed with the medical monitor prior to patient enrollment into the study. • electrocardiograms (ECGs) are to be performed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. ~~These findings can be shared with the medical monitor at the investigator's discretion.~~ • vital signs (respiratory rate and body temperature) are performed at week 16 in Study TV50717-CNS-30080, these findings will serve as day 1 baseline values in this study. ~~These findings can be shared with the medical monitor at the investigator's discretion.~~ • physical examinations are performed at week 15 (and week 16, if applicable) in Study TV50717-CNS-30080. The findings from the last assessment taken will serve as day 1 baseline	For all patients, the week 16 visit from Study TV50717-CNS-30080 may be the day 1 visit for Study TV50717-CNS-30081. Day 1 assessments for Study TV50717-CNS-30081 that are identical to Study TV50717-CNS-30080 week 15/16 visit assessments, whichever is the most current, **do not** need to be repeated, except for orthostatic pulse rate and blood pressure, which need to be repeated at day 1. In addition, the following applies for day 1 baseline assessments for this study: • clinically significant laboratory abnormalities identified at week 15 in Study TV50717-CNS-30080 are to be repeated at week 16 of the parent study for eligibility of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. Any abnormalities which are listed in the inclusion/exclusion criteria must be discussed with the medical monitor prior to patient enrollment into the study. • electrocardiograms (ECGs) are to be performed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. • vital signs (respiratory rate and body temperature) are performed at week 16 in Study TV50717-CNS-30080; these findings will serve as day 1 baseline values in this study. • physical examinations are performed at week 15 (and week 16, if applicable) in Study TV50717-CNS-30080. At the investigator's discretion, abnormal findings can be discussed with the medical monitor.	To clarify some of the day 1 procedures in Study TV50717-CNS-30081 relative to the same assessments performed at weeks 15 and 16 in the parent Study TV50717-CNS-30080

Letter of Clarification 01 text with changes shown	New wording	Reason/Justification for change
values in this study. ~~These findings can be shared with the medical monitor at the investigator's discretion.~~ At the investigator's discretion, abnormal findings can be discussed with the medical monitor. ~~For patients with new clinically significant laboratory abnormalities, electrocardiogram (ECG) results, or vital signs/physical examination findings at week 16 in Study TV50717-CNS-30080, their findings should be shared with the medical monitor and assessments should be repeated for eligibility on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study.~~		
Appendix C. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
2. Procedures Before TEV-50717 Treatment (Day 1) For all patients, the week 16 visit from Study TV50717-CNS-30080 may be the day 1 visit for Study TV50717-CNS-30081. Day 1 assessments for Study TV50717-CNS-30081 that are identical to Study TV50717-CNS-30080 baseline/week 15/16 visit assessments, whichever is the most current, **do not** need to be repeated, except for orthostatic pulse rate, blood pressure (BP), Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI-CAT), and Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) which need to be repeated at day 1. **a. Assessments carried over from Study TV50717-CNS-30080 - Baseline** • Medical history and psychiatric history • Demographics **b. Assessments carried over from Study TV50717-CNS-30080 - Week 15/16** • W16 vital signs (pulse, BP, body temperature, and respiratory rate) • W16 weight (Note: Weight must be measured		To clarify some of the day 1 procedures in Study TV50717-CNS-30081 relative to the same assessments performed at weeks 15 and 16 in the parent Study TV50717-CNS-30080

Letter of Clarification 01 text with changes shown	New wording	Reason/Justification for change
with shoes and outerwear off.) • W15 height • W16 urine drug screen • W16 urine pregnancy (beta-human chorionic gonadotropin [?-HCG]) test (required for all females who are postmenarchal or ?12 years of age) • clinically significant laboratory abnormalities identified at week 15 in Study TV50717-CNS-30080 are to be repeated at week 16 of the parent study for eligibility of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. ~~These findings are only required to be shared with the medical monitor as required per the inclusion/exclusion criteria.~~ Any abnormalities which are listed in the inclusion/exclusion criteria must be discussed with the medical monitor prior to patient enrollment into the study. • ~~electrocardiograms (ECGs) are to be performed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. These findings can be shared with the medical monitor at the investigator's discretion.~~ • ~~vital signs are performed at week 16 in Study TV50717-CNS-30080, these findings will serve as day 1 baseline values in this study. These findings can be shared with the medical monitor at the investigator's discretion.~~ • W15 physical examinations ~~are performed at week 15 (and week~~ W16, if applicable) in Study TV50717-CNS-30080. The findings from the last assessment taken will serve as day 1 baseline values in this study. ~~These findings can be shared with the medical monitor at the investigator's discretion.~~		

Letter of Clarification 01 text with changes shown	New wording	Reason/Justification for change
~~For patients with new clinically significant laboratory abnormalities, electrocardiogram (ECG) results, or vital signs/physical examination findings at week 16 in Study TV50717-CNS-30080, their findings should be shared with the medical monitor and assessments should be repeated for eligibility on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study.~~		

16.9. Letter of Clarification 02 Dated 02 July 2019

LETTER OF CLARIFICATION 02

Study Number: TV50717-CNS-30081

Clinical Study Protocol

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), Dated 07 March 2019

IND Number: 139700

1 July 2019

Dear Investigator:

The purpose of this letter of clarification is to revoke one of the changes in the previous Letter of Clarification and maintain the wording in the original protocol.

For the C-SSRS, the following is taken from Table 4 (Study Procedures and Assessments); similar wording appears in several others places in the protocol. This text will be retained in the event of a protocol amendment:

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

These changes are **not considered substantial**. Please ensure that you maintain this letter with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] at either [redacted] or [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted], Teva Pharmaceuticals

Teva Pharmaceuticals 41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. [redacted] | www.tevapharm-na.com

16.10. Letter of Clarification 01 Dated 07 June 2019

LETTER OF CLARIFICATION 01

Study Number: TV50717-CNS-30081

Clinical Study Protocol

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), Dated 07 March 2019

IND Number: 139700

7 June 2019

Dear Investigator:

This letter clarifies some of the day 1 procedures in TV50717-CNS-30081 relative to the same assessments performed at weeks 15 and 16 in the parent Study TV50717-CNS-30080.

Table 4 (Study Procedures and Assessments) in the current protocol lists the following assessments to be performed on day 1 of the study; however, these assessments are also to be performed at week 16 of the parent Study TV50717-CNS-30080. These do not need to be repeated; the data from week 16 of Study TV50717-CNS-30080 should be carried over to the current study day 1.

- vital signs and weight
- urine drug screen and β-HCG tests

In multiple places of the protocol (including Appendix C), the current text states that for patients with new clinically significant laboratory abnormalities, electrocardiogram (ECG) results, or vitals/physical examination findings at week 16 in Study TV50717-CNS-30080, these findings should be shared with the medical monitor, and assessments should be repeated for eligibility on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. The requirement for repeating assessments on day 1 (for study eligibility) has caused some confusion and will not be included in the amendment. The following details clarify the intention/requirement for each of these assessments:

- clinically significant laboratory abnormalities identified at week 15 in Study TV50717-CNS-30080 are to be repeated at week 16 of the parent study for eligibility of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. These findings are only required to be shared with the medical monitor as required per the inclusion/exclusion criteria.
- electrocardiograms (ECGs) are to be performed on day 1 of Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. These findings can be shared with the medical monitor at the investigator's discretion.

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- vital signs are performed at week 16 in Study TV50717-CNS-30080, these findings will serve as day 1 baseline values in this study. These findings can be shared with the medical monitor at the investigator's discretion.
- physical examinations are performed at week 15 (and week 16, if applicable) in Study TV50717-CNS-30080. The findings from the last assessment taken will serve as day 1 baseline values in this study. These findings can be shared with the medical monitor at the investigator's discretion.

Table 4 (Study Procedures and Assessments) in the current protocol lists the following scales to be performed on day 1 of the study; however, all of these scales are also to be performed at week 16 of the parent Study TV50717-CNS-30080. These scales do not need to be repeated; the data from week 16 of Study TV50717-CNS-30080 should be carried over to the current study day 1.

- MD-CRS part I (physician rated)
- MD-CRS part II (physician rated)
- CGI-S (global, physician rated)
- C-SSRS (children's since last visit)
- ESRS (subscales I and II)
- CBCL
- ESS

Additional nonsubstantial changes are included below with blue strikethrough indicating deleted text and red underline indicating new text.

Old Wording	New Wording	Reason for Change
Section 4.3 Withdrawal Criteria		
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 ET visit; evaluations will be as described for the week 54 visit.	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 ET visit; evaluations will be as described for the week 5<u>4</u>5 visit.	Correct typo
Section 7.5.2.1 β-HCG tests		
β-HCG tests in urine will be performed for females who are postmenarchal or ≥12 years of age at day 1 and at weeks 14, 27, and 40. β-HCG tests in serum will be performed for all female patients aged 12 years or older of childbearing potential at week 53/ET and if clinically indicated.	β-HCG tests in urine will be performed for females who are postmenarchal or ≥12 years of age at day 1 and at weeks 14, 27, ~~and~~ 40, <u>and 54</u>. β-HCG tests in serum will be performed for all female patients aged 12 years or older of childbearing potential at week 53/ET and if clinically indicated.	Corrected an omission
5.1.1.1. Starting Dose and Dose Levels		
TEV-50717 will be supplied as 20- or 60-count white tablets per dose strength per bottle.	TEV-50717 will be supplied as ~~20- or~~ 60-count ~~white~~ tablets per dose strength ~~per bottle~~. <u>Each dose strength will be a colored tablet with a marking of "SD" and the corresponding strength.</u>	Clarification

TEVA Pharmaceuticals

Old Wording	New Wording	Reason for Change
Table 4: Study Procedures and Assessments		
‡ Children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The children's C-SSRS questionnaire will only be presented to patients aged ≥12 years.	‡ Children ~~13 years of age and~~ under 13 years of age must be interviewed in conjunction with the caregiver/adult. For children 13 years of age and over, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The children's C-SSRS questionnaire will only be presented to patients aged ≥13~~2~~ years.	Clarification
APPENDIX C STUDY PROCEDURES		
• C-SSRS (Note: Children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. C-SSRS questionnaire will only be presented to patients aged ≥12 years.)	• C-SSRS (Note: ~~Children 13 years of age and under must be interviewed in conjunction with the caregiver/adult.~~ For children ~~over~~ 13 years of age and over, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. C-SSRS questionnaire will only be presented to patients aged ≥1~~2~~3 years.)	Clarification
Table 7: Investigational Medicinal Products Used in the Study		
Dosing instructions **Packaging** **Manufacturer**	~~**Dosing instructions**~~ **Packaging** ~~**Packaging**~~ **Manufacturer** ~~**Manufacturer**~~ **Storage conditions**	Correct typo

These changes are **not considered substantial** and will be incorporated into an amendment. Please ensure that you maintain this letter with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] at either [redacted] or [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted], Teva Pharmaceuticals

Teva Pharmaceuticals 41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. [redacted] | www.tevapharm-na.com

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] [redacted] Teva Pharmaceutical Industries Cell: [redacted] [redacted]
Legal Representative of the Sponsor in the EU	[redacted] Merckle GmbH, Graf-Arco-Str. 3, 89079 Ulm, Germany | Registry Court: Ulm HRB 5125 Tel: [redacted] [redacted]
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study	[redacted] Teva Pharmaceutical Industries, [redacted] [redacted] Cell: [redacted] [redacted]
Study Principal Investigator	[redacted] [redacted] Vanderbilt University Medical Center, Department of Neurology 1161 21st Avenue South A-0118 MCN Nashville, TN 37232-2551 Tel: [redacted] [redacted]
Sponsor's Representative of Global Patient Safety and Pharmacovigilance For **serious adverse events:** Send by email to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	[redacted] Teva Pharmaceutical Industries, [redacted] [redacted] Tel: [redacted] Cell: [redacted] [redacted]
Contract Research Organization	ICON plc South County Business Park Leopardstown Dublin 18, Ireland Tel: [redacted]

Central Clinical Laboratory	Q2 Solutions – Global Headquarters 5827 South Miami Blvd. Morrisville, NC 27560 Tel: [redacted]
Central Electrocardiogram Evaluation	Spaulding Medical, LLC 525 S. Silverbrook Drive West Bend, WI 53095 Tel: [redacted]
Trial Supply Management vendor	Calyx 4 Canal Street Nottingham, United Kingdom, NG1 7EH Tel: [redacted]
Bioanalytic Laboratory	[redacted] [redacted] Watson Pharma Pvt, Ltd. Seawoods Grand Central Tower 2, Level-11, Wing-E, Plot N0 R-1, Sector 40, Nerul, Navi Mumbai-400706 India Tel. No. [redacted] [redacted]
Scales and Central Reading	Signant Health 785 Arbor Way Blue Bell, PA 19422 Tel: [redacted]

APPENDIX B. INDEPENDENT DATA MONITORING COMMITTEE

During the conduct of this study, an Independent Data Monitoring Committee (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.

The IDMC will be composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, such as a statistician. The IDMC will regularly monitor safety data throughout the open-label extension study and provide recommendations whether to (1) proceed as planned, (2) perform safety-related modifications, (3) suspend study until further notice, or (4) prematurely terminate the study due to safety concerns.

Each IDMC meeting is composed of an open session, in the presence of sponsor representatives, and a closed session, with only IDMC members and the unblinded statistician. Unblinded data may be reviewed only in the closed session. Following both sessions, the IDMC reconvenes with representatives of the sponsor to review recommendations.

Following the regular or ad hoc IDMC meeting, the chairperson will deliver the IDMC recommendation form to the IDMC project manager, who will then forward the IDMC recommendation form to the sponsor clinical lead/clinical study physician or designee.

The conduct and specific details regarding the IDMC sessions are outlined in the IDMC Charter.

APPENDIX C. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. Procedures for Screening and Enrollment

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. 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.

Patients can either enroll in the study at the week 16 visit of Study TV50717-CNS-30080 or up to 4 weeks 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 (Figure 2).

2. Procedures Before TEV-50717 Treatment

2.1 Procedures for Patients Who Enroll Between 1 and <2 Weeks After Study TV50717-CNS-30080 Week 15 Visit

a. Data carried over from Study TV50717-CNS-30080 - Screening

- Demographics

b. Assessments carried over from Study TV50717-CNS-30080 - Week 15/16

- W16 vital signs (body temperature and respiratory rate). 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, these assessments will serve as day 1 baseline values in this study. Otherwise, these assessments will be performed at day 1.
- W16 weight (Note: Weight must be measured with shoes and outerwear off.)
- W15 height
- W16 urine drug screen
- clinically significant laboratory abnormalities identified at week 15 in Study TV50717-CNS-30080 are to be repeated at week 16 of the parent study for eligibility in Study TV50717-CNS-30081 and will serve as day 1 baseline values in this study. Any abnormalities which are listed in the inclusion/exclusion criteria must be discussed with the medical monitor prior to patient enrollment into the study.
- W15 physical examination (W16, if applicable). The findings from the last assessment taken will serve as day 1 baseline values in this study.

- W15 neurological examination (W16, if applicable). The findings from the last assessment taken will serve as day 1 baseline values in this study.

c. Day 1 Assessments

- obtain informed consent/assent
- review of eligibility criteria
- medical history and psychiatric history
- urine pregnancy (beta-human chorionic gonadotropin [β-HCG]) test (required for all females who are postmenarchal or ≥12 years of age)
- orthostatic blood pressure and pulse should be measured after standing for at least 3 minutes (for patients who are able to stand)
- perform 12-lead electrocardiogram (ECG) (after at least 5-minute rest in a supine or semi-supine position)
- administer the following assessments:
  - Movement Disorder-Childhood Rating Scale (MD-CRS) part I (centrally read)
  - MD-CRS part II (centrally read)
  - MD-CRS part I (physician rated, video recording)
  - MD-CRS part II (physician rated, video recording)
  - Clinical Global Impression of Severity (CGI-S)
  - Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI-CAT)
  - Child Behavior Checklist (CBCL) (for ages 6 to 18) (Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items])
  - Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS)
  - 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)
  - UHDRS-TMC (physician rated)
  - UHDRS-TMD (physician rated)
  - Canadian Occupational Performance Measure (COPM)
  - Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit (Note: 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.). If the patient turned 12 years old during or after Study TV50717-CNS-30080, but before screening or day 1 visit (whichever comes first) of Study TV50717-CNS-30081, C-SSRS baseline/screening scale will be completed.

  - Extrapyramidal Symptom Rating Scale (ESRS) subscales I and II
  - Epworth Sleepiness Scale (ESS) (for children and adolescents)
- inquire about adverse events
- review concomitant medications
- dispense TEV-50717
- contact Interactive Web Response Systems (IWRS)

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.

If all inclusion/exclusion criteria have been reviewed and are met, and the patient is eligible for treatment, he/she will be dispensed with study drug.

2.2 Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with No Clinically Significant Changes Since the Week 15 Visit of Study TV50717-CNS-30080

Patients who enroll in the study between 2 and ≤4 weeks after the Study TV50717-CNS-30080 week 15 visit with no clinically significant changes since the week 15 visit of Study TV50717-CNS-30080 will undergo the following assessments:

a. Assessments carried over from Study TV50717-CNS-30080 - Week 15/16

- W15 or W16 (whichever is the most current) chemistry, hematology, urinalysis
- W16 urine drug screen

b. Day 1 Assessments

- obtain informed consent/assent
- review of eligibility criteria
- medical history and psychiatric history
- demographics
- vital signs (orthostatic pulse and BP, body temperature, and respiratory rate)
- weight
- physical examination
- neurological examination
- height

- 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position)
- urine pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age)
- MD-CRS part I (centrally read)
- MD-CRS part II (centrally read)
- MD-CRS part I (physician rated, video recording)
- MD-CRS part II (physician rated, video recording)
- CGI-S
- PEDI-CAT
- UHDRS-TMS
- UHDRS-TMC (centrally read)
- UHDRS-TMD (centrally read)
- UHDRS-TMC (physician rated)
- UHDRS-TMD (physician rated)
- COPM
- C-SSRS Since Last Visit (Note: 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.) If the patient turned 12 years old during or after Study TV50717-CNS-30080, but before screening or day 1 visit (whichever comes first) of Study TV50717-CNS-30081, the C-SSRS baseline/screening scale will be completed.
- ESRS subscales I and II
- CBCL (for ages 6 to 18) (full assessment Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items])
- ESS (for children and adolescents)
- inquire about adverse events
- review concomitant medications
- dispense TEV-50717
- contact IWRS

If all inclusion/exclusion criteria have been reviewed and are met, and the patient is eligible for treatment, he/she will be dispensed with study drug.

For patients who enroll in the study between 2 and ≤4 weeks after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor

regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.

2.3 Procedures for Patients Who Enroll Between 2 and ≤4 Weeks After Study TV50717-CNS-30080 Week 15 Visit with Clinically Significant Changes

The patient will undergo all screening procedures. Patients who remain eligible for participation in the study will be asked to return for day 1 assessments.

a. Screening

- obtain informed consent/assent
- review of eligibility criteria
- medical history and psychiatric history
- demographics
- vital signs (pulse, BP, body temperature, and respiratory rate)
- weight
- physical examination
- neurological examination
- height
- 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position)
- chemistry, hematology, urinalysis
- urine drug screen
- serum pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age)
- C-SSRS Since Last Visit (Note: 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.) If the patient turned 12 years old during or after Study TV50717-CNS-30080, but before screening or day 1 visit (whichever comes first) of Study TV50717-CNS-30081, the C-SSRS baseline/screening scale will be completed.
- CBCL (for ages 6 to 18) (full assessment Competence Scale [Parts I to VII] and Syndrome Scale [behavioral items])
- ESS (for children and adolescents)
- inquire about adverse events
- review concomitant medications

b. Day 1

- review of eligibility criteria
- vital signs (orthostatic pulse and BP, body temperature, and respiratory rate)
- weight
- physical examination
- neurological examination
- urine pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age)
- MD-CRS part I (centrally read)
- MD-CRS part II (centrally read)
- MD-CRS part I (physician rated, video recording)
- MD-CRS part II (physician rated, video recording)
- CGI-S
- PEDI-CAT
- UHDRS-TMS
- UHDRS-TMC (centrally read)
- UHDRS-TMD (centrally read)
- UHDRS-TMC (physician rated)
- UHDRS-TMD (physician rated)
- COPM
- C-SSRS Since Last Visit (Note: 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.) If the patient turned 12 years old between screening and day 1, the C-SSRS baseline/screening scale will be completed.
- ESRS subscales I and II
- CBCL (for ages 6 to 18) Syndrome Scale (behavioral items)
- ESS (for children and adolescents)
- inquire about adverse events
- review concomitant medications
- dispense TEV-50717

- contact IWRS

If all inclusion/exclusion criteria have been reviewed and are met, and the patient is eligible for treatment, he/she will be dispensed with study drug.

For patients who enroll in the study more than 2 weeks and up to 6 months after the Study TV50717-CNS-30080 week 15 visit, the investigator is required to consult with the medical monitor regarding eligibility prior to baseline/day 1. The patient's file should include all related correspondence with the medical monitor.

3. Procedures During TEV-50717 Treatment

a. Titration Period (Weeks 1 to 7)

i. Telephone Contacts (Weeks 1, 2, 4, 5, and 6)

Patients will be contacted by telephone to evaluate adverse events. Dose adjustment will be made by the investigator after telephone contact with the patient and caregiver/parent. The following procedures/assessments will be performed via telephone contact at weeks 1, 2, 4, 5, and 6:

- evaluate/adjust TEV-50717
- administer Clinical Global Impression of Improvement (CGI-I) (Note: 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.)
- assess TEV-50717 accountability/compliance/supply status to ensure the patient has adequate tablets, inform the patient if they should titrate, and remind them to bring used and unused TEV-50717 bottles to the next in-clinic visit
- inquire about adverse events
- review concomitant medications

If a patient experiences an adverse event that is reported during a telephone contact and is probably related to TEV-50717, he or she will be brought to the clinic for evaluation. Based on the telephone evaluation, the investigator will determine whether, with the medication already provided, the patient should titrate up, stay at that dose, or reduce the dose. If additional TEV-50717 tablets are required, it would be ordered from the distributor and provided to the patient at an unscheduled visit.

ii. In-clinic Visits (Weeks 3 and 7)

The following procedures/assessments will be performed at in-clinic visits at weeks 3 and 7:

- evaluate and, if required, adjust TEV-50717 dose (see Section 5.1.1.1)
- vital signs measurements (pulse, BP, body temperature, and respiratory rate) and weight
- perform 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position)
- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)

- administer the following questionnaires:
  - CGI-I (Note: Children 13 years of age and under must be interviewed in conjunction with the caregiver. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver should be encouraged to add relevant information.)
  - C-SSRS (Note: 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. C-SSRS questionnaire will only be presented to patients aged ≥12 years.)
  - ESRS subscales I and II
  - CBCL (Syndrome Scale part only)
  - ESS
- dispense/collect TEV-50717 (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.)
- collect used and unused TEV-50717 bottles (Note: At the week 3 in-clinic visit, accountability will be performed on all bottles returned except for bottles from patients who receive 1 bottle back to complete the week 3 in-clinic evening dose. Refer to the pharmacy manual for further details.)
- assess TEV-50717 accountability/compliance/supply (Note: At the week 3 in-clinic visit, accountability will be performed on all bottles returned except for patients who receive 1 bottle back to complete the week 3 in-clinic evening dose. Refer to the pharmacy manual for further details.)
- inquire about adverse events
- review concomitant medications
- contact IWRS

b. Maintenance Period (Weeks 14 to 53/Early Termination)

i. In-clinic Visits (Weeks 14, 27, 40, and 53/Early Termination)

The following procedures/assessments will be performed at weeks 14, 27, 40, and 53/early termination (ET):

- evaluate and, if required, adjust TEV-50717 dose at weeks 14, 27, and 40
- measure vital signs (pulse, BP, body temperature, and respiratory rate); at weeks 14 and 53/ET, orthostatic BP and pulse should be measured after standing for at least 3 minutes (for patients who are able to stand)
- measure weight (Note: weight must be measured with shoes and outerwear off)
- perform full physical examination at weeks 27 and 53/ET

- perform neurological examination at week 53/ET
- measure height at weeks 27 and 53/ET
- perform 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position)
- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- perform urine drug screen at weeks 27 and 53/ET
- perform pregnancy (β-HCG) test in females who are postmenarchal or ≥12 years of age (serum test at week 53/ET and urine test at other visits)
- administer the following questionnaires:
  - MD-CRS part I (centrally read) at weeks 27 and 53/ET
  - MD-CRS part II (centrally read) at weeks 27 and 53/ET
  - MD-CRS part I (physician rated, video recording)
  - MD-CRS part II (physician rated, video recording)
  - Caregiver Global Impression of Improvement (CaGI-I) (to be assessed before all other investigator-rated scales during these visits)
  - CGI-I (Note: 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.)
  - CGI-S (Note: 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.)
  - PEDI-CAT at weeks 27 and 53/ET
  - UHDRS-TMS
  - UHDRS-TMC (centrally read) at weeks 27 and 53/ET
  - UHDRS-TMD (centrally read) at weeks 27 and 53/ET
  - UHDRS-TMC (physician rated)
  - UHDRS-TMD (physician rated)
  - COPM at weeks 27 and 53/ET
  - C-SSRS (Note: 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. C-SSRS questionnaire will only be presented to patients aged ≥12 years.)
  - ESRS subscales I and II

  - CBCL (full assessment at week 53/ET and Syndrome Scale part only on other visits)
  - ESS
- dispense TEV-50717 (weeks 14, 27, and 40)
- collect TEV-50717
- assess TEV-50717 accountability/compliance/supply
- collect used and unused TEV-50717 bottles
- inquire about adverse events
- review concomitant medications
- contact IWRS

ii. Telephone Contacts (Weeks 21, 33, and 46)

Patients will be contacted by telephone to evaluate adverse events. The following procedures/assessments will be performed via telephone contact at weeks 21, 33, and 46:

- evaluate and, if required, adjust TEV-50717 dose
- administer CGI-I (Note: 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.)
- assess TEV-50717 accountability/compliance/supply status to ensure the patient has adequate tablets and remind them to bring used and unused TEV-50717 bottles to the next in-clinic visit
- inquire about adverse events
- review concomitant medications

If a patient experiences an adverse event that is reported during a telephone contact and is probably related to TEV-50717, he or she will be brought to the clinic for evaluation. Based on the telephone evaluation, the investigator will determine whether, with the medication already provided, the patient should titrate up, stay at that dose, or reduce the dose. If additional TEV-50717 is required, it would be ordered from the distributor and provided to the patient at an unscheduled visit.

4. Procedures After TEV-50717 Treatment (Follow-Up)

a. In-clinic Visit (Week 54)

The following procedures/assessments will be performed at week 54:

- measure vital signs (pulse, BP, body temperature, and respiratory rate)
- measure weight (Note: Weight must be measured with shoes and outerwear off.)
- perform neurological examination

- perform 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position)
- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- perform urine pregnancy (β-HCG) test in females who are postmenarchal or ≥12 years of age
- administer the following questionnaires:
  - MD-CRS part I (centrally read)
  - MD-CRS part II (centrally read)
  - MD-CRS part I (physician rated, video recording)
  - MD-CRS part II (physician rated, video recording)
  - CaGI-I (to be assessed before all other investigator-rated scales during these visits)
  - CGI-I (Note: Children 13 years of age and under must be interviewed in conjunction with the caregiver. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver should be encouraged to add relevant information.)
  - CGI-S (Note: 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.)
  - UHDRS-TMC (centrally read)
  - UHDRS-TMD (centrally read)
  - C-SSRS (Note: 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. C-SSRS questionnaire will only be presented to patients aged ≥12years.)
  - ESRS subscales I and II
  - CBCL (Syndrome Scale part only)
  - ESS
- inquire about adverse events
- review concomitant medications

b. Telephone Contact (Week 55)

The following procedures/assessments will be performed at week 55:

- inquire about adverse events
- review concomitant medications

Patients who participate in the study in compliance with the protocol for at least 53 weeks of treatment will be considered to have completed the treatment. See Section 5.4 for the definition of the end of study.

For patients who complete the study or withdraw prematurely, final evaluations will be performed at an end-of-treatment visit or on the last day the patient receives the TEV-50717, or as soon as possible thereafter. Procedures for patients who withdraw prematurely from the study are described in Section 4.3. Patients should be treated with standard of care after termination of the study as appropriate.

Patients with ongoing adverse events will be monitored as described in Section 7.1.2. Otherwise, the follow-up visit will be the last study visit.

5. Unscheduled Visits

An unscheduled telephone contact may be performed at the discretion of the investigator.

An in-clinic unscheduled visit should be performed if a patient requires a dose adjustment for adverse events reported during a telephone contact. An unscheduled visit may be performed at any time during the study at the patient's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded in the patient's source document and on the CRF as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

The following procedures/assessments will be performed at all in-clinic unscheduled visits:

- evaluate and, if required, adjust TEV-50717 dose (see Section 5.1.1.1)
- measure vital signs (pulse, BP, body temperature, and respiratory rate)
- measure weight (Note: Weight must be measured with shoes and outerwear off.)
- measure height
- inquire about adverse events
- review concomitant medications
- contact IWRS

The following procedures/assessments may be performed at unscheduled visits per the investigator's discretion:

- perform physical examination
- perform neurological examination
- perform 12-lead ECG (after at least 5-minute rest in a supine or semi-supine position)
- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- perform urine drug screen
- perform a urine/serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires

  - C-SSRS (Note: 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. C-SSRS questionnaire will only be presented to patients aged ≥12 years.)
  - ESRS subscales I and II
  - CBCL (full or Syndrome Scale part only)
  - ESS
- if applicable, dispense additional TEV-50717
- collect used and unused TEV-50717 bottles
- assess TEV-50717 accountability/compliance/supply

Other procedures may also be performed at the discretion of the investigator.

APPENDIX D. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the Independent Ethics Committee (IEC)/institutional review board (IRB) and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

Important Protocol Deviations

Any deviation from the protocol 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 deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to investigational medicinal product (IMP) administration; use of prohibited medications. All important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important protocol deviation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the important protocol deviation. If such patient has already completed the study or has withdrawn early, no action will be taken, but the deviation will be recorded.

For COVID-19 updates, refer to Appendix M.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form and the study is conducted according to applicable standard operating procedures, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor(s) are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor(s) will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (CRFs and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

For COVID-19 updates, refer to Appendix M.

Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, standard operating procedures, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

APPENDIX E. ETHICS

Informed Consent/Assent

The investigator, or a qualified person designated by the investigator, should fully inform the patient and parent(s)/legally acceptable representative (as applicable) of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee (IEC)/institutional review board (IRB). All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient and parent(s)/legally acceptable representative. The patient and parent(s)/legally acceptable representative should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

A personally signed and dated informed consent form will be obtained from each parent(s)/legally acceptable representative, and a signed and dated assent form will be obtained from each patient (if the patient is able/as applicable) before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to IEC/IRB requirements. The forms will also be signed and dated by the person who conducted the informed consent discussion. The investigator will keep the original informed consent and assent forms, and copies will be given to the patients (and each parent(s)/legally acceptable representative). It will also be explained to the patients (and each parent(s)/legally acceptable representative) that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Competent Authorities and IECs/IRBs

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In case report files and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the case report file. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance, or competent authorities. Personal medical information will always be treated as confidential.

Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on trials registry websites.

APPENDIX F. BIRTH CONTROL METHODS AND PREGNANCY TESTING

Females of childbearing potential are defined as the following:

- not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- postmenarchal or ≥12 years of age

Females who are not of childbearing potential are defined as the following:

- premenarchal or being in the period of a female's life before the first menstrual period occurs

Highly effective birth control methods:

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include the following:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, and transdermal) associated with inhibition of ovulation; these should be initiated at least 1 month (for investigational medicinal products [IMPs] potentially teratogenic/genotoxic) before the first dose of IMP
- Progestogen-only hormonal contraception (oral, injectable, and implantable) associated with inhibition of ovulation; these should be initiated at least 1 month (for IMPs potentially teratogenic/genotoxic) before the first dose of IMP
- Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before day 1
- Bilateral tubal occlusion
- Vasectomized partner, provided that he is the sole sexual partner and has received medical assessment of the surgical process
- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, and post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are **not** acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency).

Unacceptable birth control methods:

Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

APPENDIX G. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient and adult(s)/caregiver, as applicable, on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of "lost to follow-up."

APPENDIX H. LIST OF ALLOWED AND PROHIBITED MEDICATIONS

Medications that are allowed, provided that conditions outlined in the table are met, are shown in Table 11. The medical monitor must be contacted if a patient is receiving (or has to begin or stop receiving during the study) a medication that is associated with QT interval corrected for heart rate (QTc) prolongation or that is a known strong cytochrome P450 (CYP) inhibitor. The addition of a strong CYP2D6 inhibitor is prohibited during the study.

Prohibited medications that are associated with QTc prolongation are listed in Table 12.

For COVID-19 updates, refer to Appendix M.

Table 11: Allowed Medications

Generic/Drug class	Condition
Stable medications	
Hormonal birth control	Must be receiving stable treatment (including dose) for at least 3 months before day 1 and anticipated to remain stable (dose and frequency) within the study duration
Antidepressants	Must be receiving stable treatment (including dose) for at least 6 weeks before screening or day 1 (whichever comes first) and anticipated to remain stable (dose and frequency) within the study duration
Benzodiazepines, trihexyphenidyl, baclofen (oral and intrathecal), tizanidine, muscle relaxants, gabapentin, levetiracetam, and carbamazepine, topiramate, and other anticonvulsants, neuroleptics, typical and atypical antipsychotics, metoclopramide	Dosing must have been stable for at least 4 weeks before screening or day 1 (whichever comes first) and anticipated to remain stable (dose and frequency) within the study duration. Any exceptions to this period of stability for these classes of drugs should be reviewed with the medical monitor, and approval for entry into the study will be required. **Note: PRN (as needed) use is prohibited.**
Botulinum toxin	May be included in the study if they have at least 2 treatments of BoNT at a regular interval (eg, every 3 to 4 months), in reasonably stable dosages and locations (subject to investigator's judgment) to treat lower limb spasticity or dystonia, and if they are expected to continue this stable regimen of BoNT injections for the duration of this study. The injection for spasticity or dystonia must be in a muscular region that is separate from the main areas affected by choreiform movement disorder. Pre-approval from the medical monitor is required for patients receiving BoNT outside of the regular interval.
Cannabis or formulations or derivatives of cannabis	Patients may be included in this study if they are using cannabis or formulations or derivatives of cannabis in relatively stable amounts, for medical purposes (where applicable according to local regulation), under the guidance, supervision, or prescription of a clinician and anticipated to remain stable (dose and frequency) within the study duration.
Additional medications allowed with preapproval from medical monitor	
Albuterol, levalbuterol	Asthma
Guaifenesin	Cold symptoms
Antihistamines	Allergies

Generic/Drug class	Condition
Melatonin	Insomnia

Table 11: Allowed Medications (Continued)

Generic/Drug class	Condition
Stable medications	
Allowed strong CYP inhibitors[a] and anticipated to remain stable (dose and frequency) within the study duration	
Bupropion	Antidepressant (aminoketone)
Stable medications allowed according to inclusion/exclusions criteria	
Fluoxetine	Antidepressant (selective serotonin reuptake inhibitor)
Paroxetine	Antidepressant (selective serotonin reuptake inhibitor)

[a] The use of these medications will affect the maximum daily dose of study medication, as shown in Table 7.
Note: Changes to the allowed medications may be permitted in the context of this study if pre-approved by the medical monitor.
BoNT=botulinum toxin; CYP=cytochrome P450; PRN=as needed.

Table 12: Prohibited QTc-Prolonging Drugs

Generic	Class/Clinical use	Note
Azithromycin	Antibiotic/bacterial infection	Patients are allowed to take up to 500 mg/day of azithromycin
Chloroquine/Mefloquine	Anti-malarial/malaria infection	
Clarithromycin[a]	Antibiotic/bacterial infection	
Domperidone	Anti-nausea/nausea	Not available in the US
Droperidol	Sedative; anti-nausea/anesthesia adjunct, nausea	
Erythromycin[a]	Antibiotic; GI stimulant; GI motility	
Moxifloxacin	Antibiotic/bacterial infection	
Sevoflurane	Anesthetic; general/anesthesia	
Probucol	Antilipemic/hypercholesterolemia	Not available in the US
Sparfloxacin	Antibiotic/bacterial infection	Not available in the US

[a] Systemic use only. Topical use is allowed.
QTc=QT interval corrected for heart rate; GI=gastrointestinal; US=United States.

APPENDIX I. TOTAL BLOOD VOLUME

Total blood volume to be collected for each patient in this study is approximately 77.5 mL.

Total Blood Volumes

Type of samples	Screening or Baseline (day 1)[a] (mL)	Weeks 3, 7, 14, 27, and 40 (mL)	Week 53/ET(mL)	Week 54 (mL)	Unscheduled (mL)
Chemistry	(1.25-3.5)	1.25-3.5	1.25-3.5	1.25-3.5	(1.25-3.5)
Hematology	(1.0-2.0)	1.0-2.0	1.0-2.0	1.0-2.0	(1.0-2.0)
β-HCG[b]	1.25-3.5	--	1.25-3.5	--	(1.25-3.5)
Prothrombin/INR	(4.5)	4.5	4.5	4.5	(4.5)
TEV-50717 concentration[c]	--	--	4.0	--	4.0
Total volume (mL) per patient		**50**	**17.5**	**10**	

[a] Not needed if taken as part of the week 15 or week 16 visit from parent Study TV50717-CNS-30080.

[b] Serum β-HCG to be performed at screening for patients who enroll between 2 and ≤4 weeks after Study TV50717-CNS-30080 week 15 visit and had a clinically significant change and for patients who enroll >4 weeks and up to 6 months after Study TV50717-CNS-30080 week 15 visit and at week 53 for all patients.

[c] 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.

β-HCG=beta human chorionic gonadotropin; ET=early termination visit; HTBZ= dihydrotetrabenazine (active metabolite); INR=International Normalized Ratio.

APPENDIX J. PRODUCT COMPLAINTS

Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical investigational medicinal product (IMP) supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

1. **Product Complaint Information Needed from the Investigational Center**

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No

- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

2. **Handling of Investigational Medicinal Product(s) at the Investigational Center(s)**

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP.

If it is determined that the investigational center must return all IMP, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

3. **Adverse Events or Serious Adverse Events Associated with a Product Complaint**

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

4. **Documenting a Product Complaint**

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

APPENDIX K. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the case report form (CRF). Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory, central image center, or electronic diary data) the results (with the exception of the cytochrome P450 2D6 [CYP2D6] genotyping results) will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, Independent Ethics Committee (IEC)/institutional review board (IRB), and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11 (US) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated, and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, and electronic patient-reported outcome tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet the eligibility criteria, at a minimum, data for screening failure reason, demography, and any serious adverse events from the time of informed consent will be entered in the CRF.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's standard operating procedures (SOPs) for clinical studies. Day-to-day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to, the following:

- full case histories
- signed informed consent forms
- patient identification lists
- CRFs for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms

- reports of receipt, use, and disposition of the investigational medicinal products
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the contract research organization or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

APPENDIX L. PUBLICATION POLICY

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements:

- substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

APPENDIX M. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19

This appendix is to address the modification in study conduct during the coronavirus disease 2019 (COVID-19) pandemic.

The changes specified in this appendix will be effective for the duration of the COVID-19 pandemic. Once the situation at specific sites/countries will allow returning to regular study activities, this appendix will become void for those country/sites, except in the case of COVID-19 resurgence or emergence of another crisis (eg, geopolitical situation) affecting normal per-protocol conduct of the study.

The following sections are affected:

Section 3.1. General Study Design and Study Schematic Diagram

A COVID-19 addendum informed consent will be created to inform patients of the planned changes. Site will be allowed to conduct remote assent and consent by phone. Site will obtain and document a verbal confirmation from patient and legally acceptable representative that they received this information and understood it. Informed Consent addendum will be signed by the patient and family as applicable at the first next in-clinic visit. Any updates prior to the updated consent form should be consented verbally and documented in the medical sources.

Section 3.5 Schedule of Study Procedures and Assessments (Tables 4 and 5)

In the event of an emergency situation (eg, the COVID-19 pandemic), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), home or remote visits are permitted for patients who are not able to go to the investigational site for their visit(s) or if the investigational site staff are not able to evaluate patients at the investigational site. All virtual visits replacing a scheduled in-clinic visit must be approved prior to proceeding by the medical monitor. After any week 3, week 7, week 14, week 27, or week 40 visit is performed remotely, the patient should come to the research site for an unscheduled visit as soon as the COVID-19 situation permits, and this plan for unscheduled visit should be discussed with the medical monitor to determine the timing and the assessments to be done. In case it is not possible, the medical monitor should be contacted and possibility of early termination of the patient may be considered based on the safety assessments.

After remote week 53/end of treatment (ET) or week 54 visits, the patient should attend a study visit at the research site as soon as the COVID-19 situation permits. All week 53/ET and week 54 assessments required in the protocol will be performed during the in-clinic visit (eg, some assessments will be repeated from the remote week 53/ET or week 54 visit).

Modifications to other procedures and assessments (electrocardiogram [ECG], laboratory sample collection, etc) will be performed per implemented contingency measures according to the Sponsor's instructions and the corresponding manual. For example, if central laboratory samples cannot be collected for safety assessments, sites may have patients visit a local laboratory to perform the assessments. At-home nursing visits may be used to perform safety assessments such

as ECG, laboratory sample collection, and other assessments to determine any new adverse events.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. The original protocol instructions should be followed whenever the new instructions are not required.

Section 4.3 Withdrawal Criteria and Procedures for the Patient

In the event of an emergency situation (eg, the COVID-19 pandemic), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), patients who cannot complete their ECG assessments during the titration period (local or at site) at week 3 and week 7 visits will be early terminated from the study. In addition, patients who cannot complete the Columbia-Suicide Severity Rating Scale (C-SSRS) and pregnancy test as per protocol will also be early terminated from the study.

In the event the patient cannot continue in the study due the current emergency situation (eg, the COVID-19 pandemic), the patient will be terminated early from the study. However, patients may be allowed to re-enter the study as soon as the current emergency situation (eg, the COVID-19 pandemic) permits, following approval by the medical monitor and full screening assessments. As a consequence, it is possible that a patient may participate in the study for longer than initially planned and, therefore, may receive treatment for more than 53 weeks.

Section 5.1.1.2 Dose Modification and Dose Stratification

In the event of an emergency situation (eg, the COVID-19 pandemic), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), patients can remain on the same dose at week 3 and week 7 for up to 2 additional weeks if the patient is tolerating investigational medicinal product (IMP) well and the medical monitor confirms the ECGs have been normal (including QTc intervals). Further titration at week 3 cannot occur until ECG, C-SSRS, and pregnancy test (as relevant) are performed and results confirmed as acceptable for continued titration. Additional IMP can be supplied to patient without the need for an in-clinic visit. The medical monitor should be contacted to approve and confirm the duration of the extension of the dosing.

If the patient is unable to come to the site at week 14, week 27, week 40, or week 53, is tolerating IMP adequately, and the medical monitor confirms the ECGs have been normal (including QTc intervals), the patient can remain on the same dose until the patient can return for an in-clinic visit, up to 4 additional weeks. If the patient is unable to return to the site at the time, the patient may be early terminated from the study at the decision of the medical monitor.

5.2. Handling, Labeling, Storage, and Accountability

IMP direct to patient delivery is being setup as long term solution and will be available in countries that support this under the COVID-19 restrictions; the common solution is to allow sites to mitigate any IMP shipment to patient according to local practice (eg, courier). Due to local regulatory restrictions, this will likely be the predominant practice.

The IMP will continue to be administered at home. Following patient's/parent's consent, IMP will be shipped to patient if his or her family cannot reach site to collect the study drug. All shipping arrangements will be the site's responsibility and will occur between site and patient.

Section 6 Assessments of Efficacy

In the event of an emergency situation (eg, the COVID-19 pandemic), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), remote assessment may be allowed for the following:

- via nonrecording live video for the Clinical Global Impression of Improvement [CGI-I] mandatory at week 3 and week 7, Clinical Global Impression of Severity [CGI-S], Movement Disorder-Childhood Rating Scale [MD-CRS] parts I and II, Unified Huntington's Disease Rating Scale-Total Motor Score [UHDRS-TMS], and the Canadian Occupational Performance Measure [COPM], as applicable. The results of the questionnaires will be entered to the case report form (CRF) per the usual process indicating that the rating has been performed remotely.
- via iPhone® (Apple, Inc) or via paper back-up copy instead of iPad® (Apple Inc) for the Caregiver Global Impression of Improvement [CaGI-I] and the Pediatric Evaluation Disability Inventory-Computer Adapted Test [PEDI-CAT], as applicable. The results of the questionnaires will be transferred to the CRF per the usual process (either from iPhone or from paper back-up copy).

The MD-CRS Part I & II are optional at the investigator's discretion and may be incomplete considering patient's imbalance when standing and walking and prioritizing patient safety. UHDRS-TMS should be completed as much as possible; some fields (ie, rigidity, stability) may be left blank as they cannot be assessed remotely. The pull test should not be done due to safety considerations.

Section 7 Assessment of Safety

In the event of an emergency situation (eg, the COVID-19 pandemic), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), remote assessment of safety scales (as well as inquiries regarding adverse events and use of concomitant medication) via teleconference and/or video conference, with video conference being the preferred method, may be allowed.

Modifications to other procedures and assessments (ECG, laboratory sample collection, etc) will be performed per implemented contingency measures according to sponsor instructions and the corresponding manual.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. The original protocol instructions should be followed whenever the new instructions are not required.

Section 7.2 Safety Rating Scales

In the event of an emergency situation (eg, the COVID-19 pandemic), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), remote assessment of safety scales may be allowed for the following:

- via a phone call, supported by nonrecording live video for the C-SSRS (mandatory) and for the Extrapyramidal Symptom Rating Scale (ESRS), which should be completed as much as possible; some fields [ie, rigidity, stability] may be left blank as they cannot be assessed remotely; the pull test should not be done due to safety

considerations. The results of the questionnaires will be entered to the case report form (CRF) per the usual process indicating that the rating has been performed remotely.

- via iPhone or via paper back-up copy instead of iPad for Child Behavior Checklist [for ages 6-18] [CBCL] and for Epworth Sleepiness Scale [for children and adolescents] [ESS].

The results of the questionnaires will be transferred to CRF per the usual process (either from iPhone or from paper back up copy).

Section 7.5 Clinical Laboratory Tests

If central laboratory samples cannot be collected for safety assessments, patients may have a home nursing visit, if available, to collect the required samples or have the patient visit a local laboratory to perform the assessments. The laboratory results will be sent to the investigator for review.

- Laboratory tests are optional at week 3 and week 14, mandatory at week 7, mandatory at week 27 and week 40 if not done at the respective previous visit, and mandatory at week 53/ET and week 54.
- Urine drug screen is optional in case laboratory tests are not mandatory.
- Urine beta-human chorionic gonadotropin (β–HCG) kits may be shipped to the patient's home when a safety laboratory test is not mandatory. Urine β–HCG test is mandatory for all visits when it is required as per protocol.

Section 7.6 Vital Signs

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.

Section 7.9 Electrocardiography

ECG is mandatory at week 3 and week 7, optional at week 14 (depending on the results of previous ECG satisfying the safety requirements per protocol), mandatory at week 27 and week 40 (if not done at the respective previous visit), and mandatory at week 53/ET and week 54. ECGs can be obtained at home or at the local clinic. The ECGs will be sent to the investigator for review and then forwarded for central assessment.

9. STATISTICS

Depending on the impact of COVID-19 on the study assessments, additional analyses or modifications of planned analyses will be considered and detailed in a possible amendment to the statistical analysis plan.

Section 10. Quality Control and Quality Assurance

Deviations from the study conduct due to emergency situations (eg, the COVID-19 pandemic), including implemented contingency measures and their impact (eg, patient discontinuation from treatment with investigational product and/or study, alternative procedures used to collect critical

safety and/or efficacy data) will be described in the appropriate sections of the clinical study report as applicable.

Appendix D. Quality Control and Quality Assurance

Important Protocol Deviations

Deviations from the study conduct due to emergency situations (eg, the COVID-19 pandemic), including implemented contingency measures and their impact (eg, patient discontinuation from treatment with investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) will be described in the appropriate sections of the clinical study report as applicable.

Study Monitoring

In case of an emergency situation (eg, the COVID-19 pandemic), monitors may not be able to access the investigational centers for on-site visits in a timely manner. A remote monitoring risk mitigation plan will be utilized for sites where on-site monitoring visits are not permitted. Details are provided in the monitoring plan.

Audit and Inspection

In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be audited remotely where allowed and in accordance with local regulations.

Appendix H. List of Allowed and Prohibited Medications

Hydroxychloroquine is contraindicated in this trial due to the risk of QT prolongation, and should be considered as not allowed. If there is a medical decision to initiate chloroquine, hydroxychloroquine, mefloquine, or other drugs related to chloroquine, the IMP should be suspended or discontinued and an ECG should be obtained. Please consult with the medical monitor for further advice.