Clinical Study Protocol

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents

Study Number TV50717-CNS-30080

NCT03813238

Protocol with Amendment 05 Approval Date: 24 March 2022

Clinical Study Protocol Amendment 05

Study Number TV50717-CNS-30080

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents

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

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

Phase 3

IND Number: 139700; NDA Number: NA; EudraCT Number: 2018-003742-17

EMA Decision Number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

Protocol Approval Date: 27 September 2018
Protocol Amendment 05 Approval Date: 24 March 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-30080 (original protocol dated 27 September 2018) has been amended and reissued as follows:

Amendment 05	24 March 2022 63 patients enrolled to date
Administrative Letter 07	05 May 2021
Amendment 04	09 March 2021 46 patients enrolled to date
Amendment 03	08 June 2020 30 patients enrolled to date
Amendment 02	17 October 2019 0 patients randomized/enrolled to date
Letter of Clarification 06	05 August 2019
Letter of Clarification 05	16 January 2019
Amendment 01	20 December 2018 0 patients randomized/enrolled to date
Letter of Clarification 04	05 December 2018
Letter of Clarification 03	22 November 2018
Letter of Clarification 02	16 November 2018
Letter of Clarification 01	17 October 2018

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 27 September 2018
Amendment 05 Dated: 24 March 2022

IND Number: 139700; NDA Number: NA; EudraCT Number: 2018-003742-17

EMA Decision Number of Pediatric Investigation Plan: Not Applicable

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A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with amendment 05 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, 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 within the Trial Master File.

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 27 September 2018
Amendment 05 Dated: 24 March 2022

IND Number: 139700; NDA Number: NA; EudraCT Number: 2018-003742-17

EMA Decision Number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents

I have read the protocol with amendment 05 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]

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**	**Date**

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

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 27 September 2018
Amendment 05 Dated: 24 March 2022

IND Number: 139700; NDA Number: NA; EudraCT Number: 2018-003742-17

EMA Decision Number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents

I have read the protocol with amendment 05 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	Signature	Date

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

CLINICAL STUDY PROTOCOL SYNOPSIS

Study TV50717-CNS-30080

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents

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: 2018-003742-17

Name of Active Ingredient: Deutetrabenazine

EMA Decision Number of Pediatric Investigation Plan: Does not apply

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

EudraVigilance code for the IMP, if applicable: SUB179485

Type of Study: Efficacy and safety study (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 60 investigational centers.

Regions Planned: North America, Asia, and Europe

Planned Study Period: Fourth quarter of 2018 to fourth quarter of 2022

Number of Patients Planned (total): Approximately 65 patients are planned to be randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 43 in the TEV-50717 group; approximately 22 in the placebo group) stratified by age at baseline (6 to <12 years; 12 through 18 years, inclusive) and region (United States [US]; non-US).

Study Population: Male and female patients, 6 through 18 years of age (inclusive) at baseline, diagnosed with DCP.

Primary and Secondary Objectives and Endpoints: The primary and secondary study objectives and measures/endpoints are the following:

Objectives	Measures/Endpoints
The **primary objective** of the study is to evaluate the efficacy of TEV-50717 to reduce the severity of dyskinetic involuntary movements associated with CP.	The primary efficacy endpoint is the change from baseline to week 15 in the MD-CRS part II total score (movement disorder severity, centrally read) (TEV-50717 versus placebo).

Objectives	Measures/Endpoints
A **secondary objective** is to evaluate the specific efficacy parameters of TEV-50717 beyond the measure of the primary objective.	The key secondary efficacy endpoints (TEV-50717 versus placebo) are the following: • MD-CRS part I total score (general assessment, centrally read) change from baseline to week 15 • CaGI-I Scale (global, caregiver rated) at week 15 • CGI-I Scale (global, physician rated) at week 15 • UHDRS-TMC (centrally read) • UHDRS-TMD (centrally read) Other efficacy measures and endpoints (TEV-50717 versus placebo) include the following: • MD-CRS part I total score (general assessment, physician rated) • MD-CRS part II total score (general assessment, physician rated) • MD-CRS Global Index (calculated from MD-CRS parts I and II total scores) • UHDRS-TMS (physician rated) • UHDRS-TMC (physician rated) • UHDRS-TMD (physician rated) • PEDI-CAT (ADL, caregiver completed, content-balanced version) • The CP module of the PedsQL (QoL, patient/caregiver) • PGI-I Scale (global, patient/caregiver) • CGI-S Scale (global, physician rated) • CaGI-I response, defined as patients who are described by the caregiver as “Much Improved” or “Very Much Improved” in the CaGI-I score • CGI-I response, defined as patients who are described as “Much Improved” or “Very Much Improved” in the CGI-I score • CGI-S response, defined as patients who have a reduction of ≥1 point in the CGI-S score • PGI-I response, defined as patients who are described as “Much Improved” or “Somewhat Improved” in the PGI-I score

Objectives	Measures/Endpoints
A **secondary objective** of the study is to evaluate the safety and tolerability of TEV-50717.	The safety variables include adverse events (and the number of patients who withdraw from the study due to adverse events), vital signs, laboratory tests (hematology, chemistry, and urinalysis), ECG measurements, CBCL, ESRS, ESS, and the children's C-SSRS.

ADL=activities of daily living; CaGI-I=Caregiver Global Impression of Improvement; CBCL=Child Behavior Checklist (for ages 6-18); CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; CP=cerebral palsy; 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); MD-CRS=Movement Disorder-Childhood Rating Scale; PEDI-CAT=Pediatric Evaluation Disability Inventory-Computer Adapted Test; PedsQL=Pediatric Quality of Life Inventory; PGI-I=Patient Global Impression of Improvement; QoL=quality of life; 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.

Exploratory Objective and Endpoint: The exploratory study objective and endpoint are the following:

Objective	Endpoint
[redacted]	[redacted]

General Study Design:

This is a Phase 3, 21-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of TEV-50717 administered as oral tablets at a starting dose of 6 mg once daily in patients (age 6 through 18 years) with DCP with predominant choreiform movement disorder, who have had CP symptoms, of a non-progressive nature, since infancy (≤2 years of age). "Predominant" in this instance indicates that the choreiform movement disorder is the main cause of impairment or distress.

The study will consist of a screening period (up to 31 days) and a double-blind treatment period including a titration period (7 weeks) and a maintenance period (8 weeks), followed by a washout period of 1 week, and a follow-up telephone contact 1 week after the washout period. Throughout the study, patients will interact regularly with investigational center personnel, in-clinic and by telephone (with non-recording live video), for the evaluation of safety/tolerability, dyskinesia severity, and behavioral status (in-clinic only).

For the purposes of this protocol, a caregiver is defined as an adult who is familiar with the patient and is 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 a legally accepted representative. In some countries, an adult (such as grandparent or nurse) can be appointed by the parent or legally accepted representative (as per local regulations and laws) and would take over this responsibility as a caregiver. The parent or legally accepted representative only has to sign the parent/legally accepted representative informed consent form (ICF) and not the caregiver ICF.

For adult patients, a caregiver must be appointed by the patient; this can be the parent, a legally accepted representative, 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 accepted representative, ie, informed consent, withdrawal of consent, requests for discontinuation of the 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 accepted representative" is specifically indicated in the protocol.

At the baseline visit (day 1), patients will be randomly assigned to 1 of 2 treatment groups with TEV-50717 IMP or placebo IMP in a 2:1 ratio stratified by age at baseline (6 to <12 years; 12 through 18 years, inclusive) and region (US; non-US). IMP will be titrated during the double-blind treatment period starting with 6 mg of TEV-50717 or matching placebo IMP in the morning of day 2. Patients in the highest body weight group (≥40 kg/88 lbs) will start an evening administration from day 3 and for the remainder of the first week. 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. The number of matching placebo IMP tablets will be increased accordingly. 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. During the titration period, the dose of IMP will be adjusted according to the titrations scheme to identify a dose level that optimally reduces dyskinesia (as determined by the investigator, as indicated by a reduction in the Clinical Global Impression of Improvement [CGI-I]) and is well tolerated. If a patient experiences a "clinically significant" adverse event attributable to the IMP, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible. After titration, patients will remain at their optimal dose for the length of the maintenance period.

Screening period (up to 31 days): After written informed consent/assent, as appropriate, is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history; physical and neurological examination; laboratory testing; 12-lead electrocardiogram (ECG); along with Movement Disorder-Childhood Rating Scale (MD-CRS) part II (physician rated, with video recording, centrally read with video review, centrally read by Enrollment Adjudication Board [EAB]) to assess severity of dyskinesia; Clinical Global Impression of Severity (CGI-S) to assess clinical impression of DCP severity, comorbid CP symptoms, and behavioral status; children's Columbia-Suicide Severity Rating Scale (C-SSRS); assessment of drug-induced parkinsonism according to the Extrapyramidal Symptom Rating Scale (subscales I and II; ESRS); assessment of change in behavior according to the Child Behavior Checklist (for ages 6-18) (CBCL) questionnaire; and assessment of sedation according to the Epworth Sleepiness Scale (for children and adolescents) (ESS) questionnaire. Screening may be conducted over 2 separate visits at the discretion of the

investigator. The diagnosis of CP and DCP will be established based on clinical features as described in the inclusion/exclusion criteria. The EAB will also confirm, based on video recordings, that choreiform is clinically the predominant movement disorder of the patient's DCP. EAB assessment results will be available to the investigator prior to baseline and randomization. The MD-CRS part II will be administered by the investigational center physician and video review, for central-blinded reading. In this study, the MD-CRS part II will be scored only based on chorea.

Titration period (7 weeks): Patients who remain eligible for participation in the study will be randomized at the baseline visit (day 1) and instructed to take the first dose of blinded IMP the following morning 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 and cytochrome P450 2D6 (CYP2D6) impairment status at baseline. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer. At the baseline visit, a telephone for non-recording live video will be provided to the patient and caregiver. Patients and their caregiver will interact weekly with the investigator/staff, either by telephone contact (with non-recording live video) or clinic visit from week 1 through week 7 of the titration period, in order to evaluate safety/tolerability and establish a dose of IMP that optimally reduces the severity of dyskinetic involuntary movements (clinically meaningful reduction in dyskinesia, as indicated by a reduction in the CGI-I) and is well tolerated. Safety/tolerability in-clinic evaluations during titration include assessment of vital signs, monitoring for adverse events and concomitant medications, 12-lead ECGs, identifying subjects at risk for suicide according to the C-SSRS questionnaire, 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. If a patient experiences a "clinically significant" adverse event attributable to the IMP, 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 dose will be established for the maintenance period. 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.

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 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. The dose of the IMP should be increased on a weekly basis to reach a clinically meaningful reduction in dyskinesia, as indicated by a reduction in the CGI-I. The IMP dose should not be increased further if either of the following occurs:

- the patient experiences a protocol-defined "clinically significant" adverse event (defined as an adverse event that is related to IMP 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 baseline.

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 IMP should not be increased further, but the patient should continue on that dose for the remainder of the titration period and throughout

the maintenance period. If a patient experiences a "clinically significant" adverse event attributable to the IMP, 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.

Maintenance period (8 weeks): Patients will continue to receive their maintenance dose over the next 8 weeks, although a 1-time dose reduction (to the previous dose level for the remainder of the study) for adverse events is allowed. Patients will return to the clinic at weeks 9, 12, and 15 for assessments of efficacy and safety.

Washout period and follow-up: All patients will discontinue IMP at the week 15 visit and will return 1 week later for the end-of-study visit. Patients who complete the study may be eligible to begin participation in the open-label safety extension Study TV50717-CNS-30081 at that time. At the week 16 visit, patients may choose to enter Study TV50717-CNS-30081 (on that day) or up to 1 week later (2 weeks from the week 15 visit). Patients who complete treatment but choose not to participate in the open-label safety extension Study TV50717-CNS-30081 any time before week 17 of Study TV50717-CNS-30080 will be contacted for a safety evaluation call occurring 2 weeks after their last dose of IMP. Additional details for patients to enter Study TV50717-CNS-30081 are provided in the TV50717-CNS-30081 protocol.

When approximately 50 patients have completed the study (including follow-up), an independent Data Monitoring Committee (iDMC) will perform an unblinded non-binding interim analysis (IA) for futility based on centrally read MD-CRS part II total score.

An iDMC charter will be developed for the IA, and the procedures to ensure the integrity of the study will be provided in the charter.

At the time of informed consent, the parent/legally accepted representative will be counseled that, once randomized to treatment, patients are to remain in the study and complete all study procedures unless the choice is made to withdraw consent. Patients who withdraw from the study before completing the 15-week treatment period should have an early termination (ET) visit as soon as possible after the last dose of IMP. All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after ET; evaluations will be as described for week 17.

Patients who screen fail or terminate early from the study due to emergency circumstances (such as coronavirus disease 2019 [COVID-19]) may be allowed to re-screen/re-enter (respectively) the study at a later date, depending on the circumstances. Each case should be referred to the medical monitor and approved in advance.

There is a separate protocol for the open-label safety extension Study TV50717-CNS-30081.

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

CP refers to a group of neurological disorders that appear in infancy or early childhood and permanently affect body movement and muscle coordination. CP is caused by damage to or abnormalities inside the developing brain that disrupt the brain's ability to control movement and maintain posture and balance. The signs of CP usually appear in the early months of life, although specific diagnosis may be delayed until the age of 2 years or older. TEV-50717 (deutetrabenazine, also known as SD-809) has already provided evidence for safe and effective

use in 2 other hyperkinetic movement disorders, namely chorea in Huntington's disease (HD) and tardive dyskinesia (TD). Currently, there is no approved treatment available for DCP. 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) with DCP with predominant choreiform movement disorder, who have had non-progressive CP symptoms since infancy (≤2 years of age). Diagnosis of DCP is based on the Surveillance of Cerebral Palsy in Europe criteria.

This is a Phase 3 study that will evaluate the efficacy and safety of TEV-50717 administered as oral tablets at a starting dose of 6 mg once daily in patients (age 6 through 18 years, inclusive) with DCP with predominant choreiform movement disorder. The study will be conducted in multiple centers and will use 2 parallel treatment groups (ie, TEV-50717 and placebo) in which patients will be randomized in a 2:1 ratio.

Method of Randomization and Blinding:

Patients will be randomly assigned to receive treatment with TEV-50717 or matching placebo in a 2:1 ratio using Randomization and Trial Supply Management (RTSM). Patients will be stratified by age at baseline (6 to <12 years; 12 through 18 years, inclusive) and region (US; non-US). Patients and investigators will remain blinded to treatment assignment during the study. In addition, the sponsor's clinical personnel and all vendors (with the exception of the sponsor's clinical supply chain staff and RTSM vendor) will be blinded to the IMP identity until the database has been locked for analysis and the treatment assignments are revealed.

The iDMC will perform an unblinded non-binding IA for futility and will monitor safety throughout the study based on unblinded data. An iDMC charter will be developed for the IA, and the procedures to ensure the integrity of the study will be provided in the charter.

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

The IMPs are defined as the test IMP and placebo IMP. There is no reference IMP in this study.

Test IMP 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 baseline are shown in Table 1. The maximum daily dose is determined by body weight at baseline and CYP2D6 impairment status (Table 2). Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer. Although dose adjustments can be made up to and including the week 7 in-clinic visit, if the optimal dose is reached before then, the dose of IMP should not be increased any further, but the patient should continue taking that dose for the remainder of the titration period and throughout the maintenance period. If a patient experiences a "clinically significant" adverse event that is attributed to the IMP, 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 dose will be established for the maintenance period. If a patient experiences an adverse event during the maintenance period and the investigator believes a dose reduction is warranted, the dose may be reduced once for the remainder of the maintenance period.

TEV-50717 tablets (test IMP) are available in the following dose strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). Test IMP will be supplied in

20-count tablets per dose strength per bottle assembling 6, 12, 18, 24, 30, 36, 42, and 48 mg dose kit combinations.

The placebo IMP tablets and packaging will match those for TEV-50717.

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.

IMP will be administered as follows:

- IMP should be swallowed whole. If the IMP is crushed or split, it should not be ingested; it should be replaced with a new tablet. The tablets will 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 will be based on body weight at the baseline visit and CYP2D6 impairment status, as shown in Table 1 and Table 2, respectively.
- If there is only a single dose of IMP per day, the dose should be taken in the morning. However, patients experiencing somnolence while taking the 6-mg dose in the morning may switch to taking it as an evening dose for the rest of the days up to day 14.
- The starting dose of 6 mg will be administered in the morning on day 2 and for the remainder of the first week. Patients in the highest body weight group (≥40 kg/88 lbs) will start an evening administration from day 3 and for the remainder of the first week. 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.
- 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.
- During the week 3 visit, the investigator or designee will make sure the patient receives the last treatment kit back so the patient can take 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 IMP should be adjusted according to Table 1 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 telephone or in-clinic visit.

Table 1: Maximum Daily Dose of IMP During the Titration Period by Week and Weight Category at Baseline

	Daily dose[a,b]			
Study time period	**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[d]	18 mg[d]	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 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 3 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, or those who are poor CYP2D6 metabolizers, 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 2).
CYP2D6=cytochrome P450 2D6; IMP=investigational medicinal product.

Table 2: Maximum Daily Dose of IMP 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; IMP=investigational medicinal product.
Note: Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer. Strong CYP2D6 inhibitors include paroxetine, fluoxetine, and bupropion.

Test IMP: TEV-50717 (deutetrabenazine, also known as SD-809)

Reference IMP: None

Placebo IMP: Placebo tablets match TEV-50717 (deutetrabenazine, also known as SD-809)

Duration of Patient Participation and Maximal Exposure to IMP:

This study will consist of up to a 31-day screening period, a 15-week double-blind treatment period (a 7-week titration period followed by an 8-week maintenance period), and a 2-week follow-up period. Patients are expected to participate in this study for its entire duration.

Study Duration: Fourth quarter of 2018 to fourth quarter of 2022

End of Study: End of study is defined as the last visit of the last patient.

Plans for Treatment or Care After the Patient Has Ended Participation in the Study: Patients who complete the study may be eligible to begin participation in the open-label safety extension Study TV50717-CNS-30081 at the end of the washout period. Patients who complete treatment, but choose not to participate in the open-label safety extension Study TV50717-CNS-30081 any time before week 17 of Study TV50717-CNS-30080 will be contacted for a safety evaluation call occurring 2 weeks after their last dose of IMP.

Inclusion Criteria: Patients may be included in the study only if they meet all of the following criteria:

1. Patient is 6 through 18 years of age (inclusive) at baseline.
2. Patient weighs at least 26 pounds (12 kg) at baseline.
3. Patient has had CP symptoms since infancy (≤2 years), and CP is judged by the investigator to be of a non-progressive nature (Monbaliu et al 2017, Wimalasundera et al 2016).
4. Patient has a diagnosis of DCP according to the Surveillance of Cerebral Palsy in Europe criteria (Cans 2000).
5. Patient has an MD-CRS part II total score of ≥10 at the baseline visit, based on investigator scoring of chorea.
6. Patient's symptoms are causing functional problems determined by a CGI-S score of 4 or greater based on investigator scoring.
7. Choreiform is the predominant (ie, the main cause of impairment or distress) movement disorder as assessed at screening.
8. Patient is able to swallow study medication whole.
9. Patient and caregiver are willing to adhere to the medication regimen and to comply with all study procedures.
10. Patient is in good general health, as indicated by medical and psychiatric history, as well as physical and neurological examination.

11. 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.
12. For a patient who is a minor, the parent(s)/legally accepted representative(s) provide written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide their own written informed consent (in accordance with local regulations) and the legally acceptable representative will sign, if needed.

    In this study, eligible patients are patients with dyskinetic cerebral palsy who 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.
13. Caregivers provide written informed consent after being assigned the role by an adult patient, or if this role is delegated by the parent/legally accepted representative of a patient who is a minor.
14. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative beta-human chorionic gonadotropin test at baseline or are sterile. Definitions of sterile, premenarchal, and postmenarchal are given in Appendix F.
15. 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 screening) and for 30 days after the last dose of IMP. Further details are included in Appendix F.

Exclusion Criteria: Patients will be excluded from participating in this study if they meet any of the following criteria:

1. 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.
   e. Patient has choreiform movement disorder that has not been consistent throughout the life of the patient.
2. Patient has clinically significant depression at screening or baseline.
   - Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening and anticipated to remain stable (dose and frequency) within the study duration.
3. Patient has a history of suicidal intent or related behaviors based on medical or psychiatric history or the C-SSRS within 2 years of screening:
   - 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

4. Patient has a history of a previous actual, interrupted, or aborted suicide attempt based on medical or psychiatric history or the C-SSRS.
5. Patient has a first-degree relative who has completed suicide.
6. Patient has received any of the following concomitant medications within the specified exclusionary windows of screening:
   - Within 30 days: tetrabenazine, deutetrabenazine, or valbenazine
   - Within 21 days: reserpine
   - Within 14 days: levodopa, dopamine agonists, and monoamine oxidase inhibitors
7. Patient has received treatment with stem cells, deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation for treatment of abnormal movements or CP within 6 months of the screening visit, or the patient is not in a stable clinical condition.
8. Patient has recent surgical procedure 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.
9. Patient has a severe mental disability or an unstable or serious medical illness (eg, epilepsy) at screening or baseline that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.
10. Patient has a QT interval corrected for heart rate using Fridericia's formula value >450 msec on 12-lead ECG at screening.
11. Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, other cardiac arrhythmias, or uncompensated heart failure.
12. Patient has evidence of diminished hepatic function, as indicated by the following:
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5× the upper limit of the normal range (ULN) at screening
    - Alkaline phosphatase (ALP) or total bilirubin >2× ULN at screening
    - 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 the following clinical laboratory parameters must be approved for enrollment by the medical monitor: AST, ALT, ALP, and total bilirubin.
13. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5 × ULN at screening.
14. Patient has a known allergy to any of the components of the IMP.
15. Patient has participated in an investigational drug or device study and received IMP/intervention within 30 days or 5 drug half-lives of screening, whichever is longer.

16. Patient is pregnant or breastfeeding.
17. Patient has a history of or acknowledges alcohol or other substance abuse in the 12 months before screening.
18. Patient has a positive urine drug screen test result (with exception of medications listed in Table 10 of Appendix H). Any request to include a patient with a positive urine drug screen test result should be discussed with, and approved by, the medical monitor. Refer to Section 7.5.2.2 (urine drug screen) for more details.

Statistical Considerations

Primary and Secondary Estimands:

The primary estimand is the difference in means between TEV-50717 and placebo in the target patient population for the change from baseline to week 15 in centrally read MD-CRS part II total score, regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events.

The secondary estimands are the differences in means between TEV-50717 and placebo in the target patient population for (1) change from baseline to week 15 in centrally read MD-CRS part I total score, (2) Caregiver Global Impression of Improvement (CaGI-I) at week 15, (3) CGI-I at week 15, (4) change from baseline to week 15 in centrally read UHDRS-TMC, and (5) change from baseline to week 15 in centrally read UHDRS-TMD, regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events.

The primary estimand assesses the effectiveness in the reduction of choreiform movements in patients with DCP with predominant choreiform movement disorder, evaluated by the central reviewers, focusing on the causal effects attributable to the IMP. The secondary estimands assess the effectiveness on patients' ability to perform daily functions, the improvement in dyskinesia evaluated by the caregiver and the investigator, and the reduction in chorea and dystonia evaluated by the central reviewers, all with a focus on the causal effects attributable to the IMP.

The patient population for this study is patients with DCP with predominant choreiform movement disorder and severity of DCP represented by MD-CRS part II total score of ≥10 and CGI-S ≥4 at baseline. This population is expected to have the sensitivity to demonstrate clinically meaningful improvement following treatment with TEV-50717. Due to practical reasons, it is not possible to obtain a central reading of MD-CRS part II items at the time of the baseline visit prior to randomization; therefore, inclusion of a subject into the study is based on investigator scoring of MD-CRS part II items at baseline.

Analysis of Primary Endpoint:

The primary endpoint is the change from baseline to week 15 in centrally read MD-CRS part II total score (TEV-50717 versus placebo). The MD-CRS part II total score is obtained by summing the total raw scores of MD-CRS part II items (0 to 28).

The modified intent-to treat (mITT) analysis set (all randomized patients with at least 1 post-baseline centrally read MD-CRS part II assessment) will be used for the primary analysis.

The primary analysis will be a mixed-model, repeated-measures with the change in MD-CRS part II total score as the dependent variable. The model will include fixed effects for treatment

group, week (3 levels: weeks 9, 12, and 15), and treatment group by week interaction. The baseline MD-CRS part II total score, age group at baseline (2 levels: 6 to <12 years; 12 through 18 years, inclusive), and region (US; non-US) will be included as covariates. The unstructured covariance model will be used.

Missing data will be classified as missing at random (MAR) and missing not at random (MNAR). Early terminations related to tolerability, treatment-related adverse events, or lack of efficacy will be classified as MNAR. Intermittent missing data, early terminations for patients who are lost to follow-up, and early terminations due to COVID-19 will be classified as MAR. For all other cases and for cases classified as above, classification as MAR/MNAR will be done/revisited in a blinded manner on a case-by-case basis prior to the IA and prior to database lock for final analysis. The MAR/MNAR multiple imputation method will be applied in the primary analysis, where MNAR data will be imputed using the jump-to-reference method, and MAR data will be imputed based on the randomized treatment group. The resulting complete, imputed datasets will each be analyzed using the analysis model described above, and the resulting statistics combined using methodology presented by Rubin (1987) and Little and Rubin (2002).

The difference in least squares (LS) mean of the change in MD-CRS part II total score from baseline to week 15 (TEV-50717 versus placebo) will be compared using a 1-sided test for superiority at a nominal significance level of α=0.025.

The LS mean and standard error for the treatment groups, the LS mean difference, 2-sided 95% confidence interval, and p-value for the comparison (TEV-50717 versus placebo) at week 15 will be presented.

Sample Size Rationale:

The initial sample size estimation of approximately 185 patients randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 124 in the TEV-50717 group; approximately 61 in the placebo group) is the sample size required to obtain a statistically significant result in the primary analysis based on a 1-sided test for mean difference at a significance level of α=0.025 with a power of approximately 90%, assuming a mean difference of 1.8 and a standard deviation (SD) of 3.5 in each treatment group.

At the time of writing Amendment 05, the initially planned sample size has been reduced to approximately 65 patients randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 43 in the TEV-50717 group; approximately 22 in the placebo group).

The initial assumptions regarding the mean difference and SD are based on the change from baseline to month 6 in patients treated with trihexyphenidyl reported by Battini et al (2014), assuming an effect size of 55% for TEV-50717 versus placebo. The effect size of 55% was assumed based on the observed effect sizes of TEV-50717 in the pivotal studies in HD and TD. In the current study, these assumptions correspond to a mean difference of 2.0 in MD-CRS part II total score and an SD of 3.5 in each treatment group.

The rate of MNAR data for the primary analysis is expected to be 10%. MNAR data will be imputed in a conservative manner as if they were obtained from patients in the placebo treatment group, regardless of the treatment group. As a result, the mean difference is expected to be reduced from 2.0 to 1.8 in the primary analysis. The impact of the missing data imputation on the SD is negligible.

Sensitivity Analysis:

To assess the robustness of the primary efficacy analysis, sensitivity analyses will include the following:

Sensitivity analyses for assumptions of missing data mechanism:

- tipping point (MNAR)
- MAR multiple imputation

Sensitivity analysis for the statistical model:

- analysis of covariance (ANCOVA)
- primary model, including only the following covariates: treatment group, week, and treatment group by week interaction

Other:

- primary model repeated for the intent-to-treat (ITT) analysis set
- primary model repeated for the set of patients in the mITT analysis set that received at least 1 dose of IMP
- primary model repeated for the set of patients that complete the study without any major protocol deviations that may impact efficacy (per-protocol analysis)
- ANCOVA models for MD-CRS part II total score change from baseline to week 9 and to week 12

Key Secondary Endpoints and Analysis:

The key secondary endpoints are the following:

1. Change from baseline to week 15 in centrally read MD-CRS part I total score (TEV-50717 versus placebo)
2. CaGI-I at week 15 (TEV-50717 versus placebo)
3. CGI-I at week 15 (TEV-50717 versus placebo)
4. Change from baseline to week 15 in centrally read UHDRS-TMC (TEV-50717 versus placebo)
5. Change from baseline to week 15 in centrally read UHDRS-TMD (TEV-50717 versus placebo)

Each key secondary endpoint will be analyzed in the same fashion as the primary endpoint, with the exception that the baseline value of the given endpoint will be included as the covariate.

Other Efficacy Measures/Endpoints:

Other efficacy measures and endpoints (TEV-50717 versus placebo) include the following:

- MD-CRS part I total score (general assessment, physician rated)
- MD-CRS part II total score (general assessment, physician rated)
- MD-CRS Global Index (calculated from MD-CRS parts I and II total scores)

- UHDRS-TMS (physician rated)
- UHDRS-TMC (physician rated)
- UHDRS-TMD (physician rated)
- Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI-CAT) (activities of daily living, caregiver completed, content-balanced version)
- The CP module of the Pediatric Quality of Life Inventory (PedsQL) (quality of life, patient/caregiver)
- Patient Global Impression of Improvement Scale ([PGI-I] global, patient/caregiver)
- Clinical Global Impression of Severity ([CGI-S], global, physician rated)
- CaGI-I response, defined as patients who are described by the caregiver as "Much Improved" or "Very Much Improved" in the CaGI-I score
- CGI-I response, defined as patients who are described as "Much Improved" or "Very Much Improved" in the CGI-I score
- CGI-S response, defined as patients who have a reduction of ≥1 point in the CGI-S score
- PGI-I response, defined as patients who are described as "Much Improved" or "Somewhat Improved" in the PGI-I score

Analysis methods will be provided in the statistical analysis plan.

Multiple Comparisons and Multiplicity:

The primary efficacy endpoint will be tested at the 1-sided significance level of α=0.025.

If the primary endpoint is statistically significant (p-value ≤0.025), the 5 key secondary hypotheses will be tested using a hierarchical approach at the 1-sided significance level of α=0.025, in the following order: (1) MD-CRS part I total score, (2) CaGI-I, (3) CGI-I, (4) UHDRS-TMC centrally read, and (5) UHDRS-TMD centrally read.

[redacted]

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

Planned Interim Analysis:

When approximately 50 patients have completed the study (including follow-up), an iDMC will perform an unblinded non-binding IA for futility based on centrally read MD-CRS part II total score.

Safety Analyses:

Safety analyses will be performed on the safety analysis set.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. 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 (overall and by severity), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory, ECG, and vital signs measurements data will be summarized descriptively. ECG and vital signs values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics.

The frequency and severity of suicidal ideation or behavior according to the children's Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire will be presented by visit and by treatment group. A shift table for children's C-SSRS categories at baseline, 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.

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

Tolerability Analysis:

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

Pharmacokinetic/Pharmacodynamic Analysis:

[redacted]

Biomarker Analysis: Not applicable

Immunogenicity Analysis: Not applicable

Ancillary Studies Analysis: Not applicable

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADL	activities of daily living
AIMS	Abnormal Involuntary Movements Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BoNT	botulinum neurotoxin
CDMS	clinical data management system
CFR	Code of Federal Regulations
CaGI-I	Caregiver Global Impression of Improvement
CBCL	Child Behavior Checklist (for ages 6-18)
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
ClinRO	clinician-reported outcome
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
EAB	Enrollment Adjudication Board
ECG	electrocardiogram
ESRS	Extrapyramidal Symptom Rating Scale (subscales I and II)
ESS	Epworth Sleepiness Scale (for children and adolescents)
ET	early termination
EOS	end of study
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

Abbreviation	Term
GPSP	Global Patient Safety and Pharmacovigilance
β-HCG	beta-human chorionic gonadotropin
HD	Huntington's disease
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
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
LS	least squares
LSO	local safety officer
MAOI	monoamine oxidase inhibitor
MAR	missing at random
MD-CRS	Movement Disorder-Childhood Rating Scale
mITT	modified intent-to-treat
MMRM	mixed-effects model repeat measurement
MNAR	missing not at random
n	number
NDA	New Drug Application
PEDI-CAT	Pediatric Evaluation Disability Inventory-Computer Adapted Test
PedsQL	Pediatric Quality of Life Inventory
PGI-I	Patient Global Impression of Improvement
PGx	pharmacogenetics
PND	postnatal day
PP	per-protocol
QoL	quality of life
QTc	QT corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
SAP	statistical analysis plan

Abbreviation	Term
SD	standard deviation
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
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
USA	United States of America
VMAT2	vesicular monoamine transporter type 2
α-HTBZ	alpha-dihydrotetrabenazine
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 (Maenner et al 2016, Monbaliu et al 2017, CDC, Prevalence of Cerebral Palsy). 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).

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 (Monbaliu et al 2017, CDC).

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 TEV-50717 is 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. IMP tablets are available in the following dose strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). The investigational medicinal product (IMP) will be supplied in 20-count tablets per dose strength 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 2015). 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

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.

This is the first study to assess the safety and efficacy of 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.

1.3. 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 the study is to evaluate the efficacy of TEV-50717 to reduce the severity of dyskinetic involuntary movements associated with CP.	The primary efficacy endpoint is the change from baseline to week 15 in the MD-CRS part II total score (movement disorder severity, centrally read) (TEV-50717 versus placebo).
A **secondary objective** is to evaluate the specific efficacy parameters of TEV-50717 beyond the measure of the primary objective.	The key secondary efficacy endpoints (TEV-50717 versus placebo) are the following: • MD-CRS part I total score (general assessment, centrally read) change from baseline to week 15 • CaGI-I Scale (global, caregiver rated) at week 15 • CGI-I Scale (global, physician rated) at week 15 • UHDRS-TMC (centrally read) • UHDRS-TMD (centrally read) Other efficacy measures and endpoints (TEV-50717 versus placebo) include the following: • MD-CRS part I total score (general assessment, physician rated) • MD-CRS part II total score (general assessment, physician rated) • MD-CRS Global Index (calculated from MD-CRS parts I and II total scores) • UHDRS-TMS (physician rated) • UHDRS-TMC (physician rated) • UHDRS-TMD (physician rated) • PEDI-CAT (ADL, caregiver completed, content-balanced version) • The CP module of the PedsQL (QoL, patient/caregiver)

Objectives	Measures/Endpoints
	• PGI-I Scale (global, patient/caregiver) • CGI-S Scale (global, physician rated) • CaGI-I response, defined as patients who are described by the caregiver as "Much Improved" or "Very Much Improved" in the CaGI-I score • CGI-I response, defined as patients who are described as "Much Improved" or "Very Much Improved" in the CGI-I score • CGI-S response, defined as patients who have a reduction of ≥1 point in the CGI-S score • PGI-I response, defined as patients who are described as "Much Improved" or "Somewhat Improved" in the PGI-I score
A **secondary objective** of the study is to evaluate the safety and tolerability of TEV-50717.	The safety variables include adverse events (and the number of patients who withdraw from the study due to adverse events), vital signs, laboratory tests (hematology, chemistry, and urinalysis), ECG measurements, CBCL, ESRS, ESS, and the children's C-SSRS.

ADL=activities of daily living; CaGI-I=Caregiver Global Impression of Improvement; CBCL=Child Behavior Checklist (for ages 6-18); CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; CP=cerebral palsy; 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); MD-CRS=Movement Disorder-Childhood Rating Scale; PEDI-CAT=Pediatric Evaluation Disability Inventory-Computer Adapted Test; PedsQL=Pediatric Quality of Life Inventory; PGI-I=Patient Global Impression of Improvement; QoL=quality of life; UHDRS-TMC=Unified Huntington's Disease Rating Scale-Total Maximal Chorea; UHDRS-TMD=Unified Huntington's Disease Rating Scale-Total Maximal Dystonia; UHDRS-TMS=Unified Huntington's Disease Rating Scale-Total Motor Score.

2.1.1. Justification of Primary Endpoint

The rationale to use a movement disorder scale as the primary endpoint to evaluate patients with DCP is based on a few key drivers. In prior studies, the motor scales measured and demonstrated a treatment benefit of TEV-50717 in patients with abnormal movements (eg, chorea and dyskinesia) associated with HD (Unified Huntington's Disease Rating Scale [UHDRS]-Total Maximal Chorea [TMC]) and TD (Abnormal Involuntary Movements Scale [AIMS]) (Austedo Prescriber Information). Moreover, the use of motor scales as a primary outcome measure has been sufficient for TEV-50717 to gain regulatory approval to treat patients with abnormal movements. Conversely, the functional and global scales did not consistently show a treatment benefit of TEV-50717 in patients with abnormal movements.

The Movement Disorder-Childhood Rating Scale (MD-CRS) part II is similar to UHDRS-TMC and AIMS in assessing the severity of abnormal hyperkinetic movement disorders in the 7 body regions using a 0 to 4 scale. Neither MD-CRS part II nor AIMS differentiates whether the

dyskinesia is dystonic or choreiform. Experts in the field support the choice of MD-CRS part II to assess the severity of movement disorders in children with DCP.

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 the severity of the movement disorder.

MD-CRS part II evaluates the severity of the movement disorder in 7 body regions, all areas in which dyskinesia can be seen in patients with CP. 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 MD-CRS part II was developed and validated in the CP population for children and adolescents aged 4 to 18 years (Battini et al 2008). In addition, the scale 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).

The MD-CRS was developed based on centralized readings of the video recordings of the patient assessments. The use of blinded centralized readings and ratings of videos of patients with movement disorders in clinical trials may decrease the inter-site and intra-site variability of data. This clinical trial will use centralized ratings of the videos to reduce data variability.

2.1.2. Primary and Secondary Estimands

The primary estimand is the difference in means between TEV-50717 and placebo in the target patient population for the change from baseline to week 15 in centrally read MD-CRS part II total score, regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events.

The secondary estimands are the differences in means between TEV-50717 and placebo in the target patient population for (1) change from baseline to week 15 in centrally read MD-CRS part I total score, (2) Caregiver Global Impression of Improvement (CaGI-I) at week 15, (3) Clinical Global Impression of Improvement (CGI-I) at week 15, (4) change from baseline to week 15 in centrally read UHDRS-TMC, and (5) change from baseline to week 15 in centrally read UHDRS-TMD, regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events.

The primary estimand assesses the effectiveness in the reduction of choreiform movements in patients with DCP with predominant choreiform movement disorder, as evaluated by the central reviewers, focusing on the causal effects attributable to the IMP. The secondary estimands assess the effectiveness on patients' ability to perform daily functions, the improvement in dyskinesia evaluated by the caregiver and the investigator, and the reduction in chorea and dystonia evaluated by central reviewers, all with a focus on the causal effects attributable to the IMP.

2.2. Exploratory Objectives and Endpoints

The exploratory study objective and endpoint of this study are the following:

Objective	Endpoint
[redacted]	[redacted]

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a Phase 3, 21-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of TEV-50717 administered as oral tablets at a starting dose of 6 mg once daily in patients (age 6 through 18 years, inclusive) with DCP with predominant choreiform movement disorder, who have had CP symptoms, of a non-progressive nature, since infancy (≤2 years of age). "Predominant" in this instance indicates that the choreiform movement disorder is the main cause of impairment or distress.

The study will consist of a screening period (up to 31 days) and a double-blind treatment period including a titration period (7 weeks) and a maintenance period (8 weeks), followed by a washout period of 1 week, and a follow-up telephone contact 1 week after the washout period. Throughout the study, patients will interact regularly with investigational center personnel, in-clinic and by telephone (with non-recording live video), for the evaluation of safety/tolerability, dyskinesia severity, and behavioral status (in-clinic only). Every effort should be made to utilize the same investigator to perform assessments on a patient throughout the duration of the study during these interactions. Under circumstances that require or encourage involvement of the patient's caregiver when administering assessments, every effort should be made to involve the same caregiver of a patient throughout the duration of the study. Standard of care for treatment of CP should continue throughout the study, with some possible restrictions. Standard of care could include any possible rehabilitation service(s), such as physiotherapy, occupational therapy, or sensory integration of the patient, should remain constant throughout the course of the study.

For the purposes of this protocol, a caregiver is defined as an adult who is familiar with the patient and is 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 a legally accepted representative. In some countries, an adult (such as grandparent or nurse) can be appointed by the parent or legally accepted representative (as per local regulations and laws) and would take over this responsibility as a caregiver. The parent or legally accepted representative only has to sign the parent/legally accepted representative informed consent form (ICF) and not the caregiver ICF.

For adult patients, a caregiver must be appointed by the patient; this can be the parent, a legally accepted representative, 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 accepted representative, ie, informed consent, withdrawal of consent, requests for discontinuation of the 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 accepted representative" is specifically indicated in the protocol.

At the baseline visit (day 1), patients will be randomly assigned to 1 of 2 treatment groups with TEV-50717 IMP or placebo IMP in a 2:1 ratio stratified by age at baseline (6 to <12 years; 12 through 18 years, inclusive) and region (US; non-US). IMP will be titrated during the double-blind treatment period starting with 6 mg of TEV-50717 or matching placebo IMP in the morning of day 2. Patients in the highest body weight group (≥40 kg/88 lbs) will start an evening administration from day 3 and for the remainder of the first week. 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. The number of matching placebo IMP tablets will be increased accordingly. 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. During the titration period, the dose of IMP will be adjusted according to the titrations scheme (details are given in Section 5) to identify a dose level that optimally reduces dyskinesia (as determined by the investigator, as indicated by a reduction in the clinician-reported outcome [ClinRO] of the assessment of the CGI-I) and is well tolerated. If a patient experiences a "clinically significant" adverse event attributable to the IMP, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible (Section 5.8). After titration, patients will remain at their optimal dose for the length of the maintenance period.

Screening period (up to 31 days): After written informed consent/assent, as appropriate, is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history; physical and neurological examination; laboratory testing; 12-lead ECG; along with MD-CRS part II (physician rated, with video recording, centrally read with video review, centrally read by the Enrollment Adjudication Board [EAB]) to assess severity of dyskinesia; Clinical Global Impression of Severity (CGI-S) to assess global clinical impression of DCP severity, comorbid CP symptoms, and behavioral status; children's Columbia-Suicide Severity Rating Scale (C-SSRS); assessment of drug-induced parkinsonism according to the Extrapyramidal Symptom Rating Scale (subscales I and II; ESRS); assessment of change in behavior according to the Child Behavior Checklist (for ages 6-18) (CBCL) questionnaire; and assessment of sedation according to the Epworth Sleepiness Scale (for children and adolescents) (ESS) questionnaire. Screening may be conducted over 2 separate visits at the discretion of the investigator. The diagnosis of CP and DCP will be established based on clinical features as described in the inclusion/exclusion criteria. The EAB will also confirm, based on video recordings, that choreiform is clinically the predominant movement disorder of the patient's DCP. EAB assessment results will be available to the investigator prior to baseline and randomization. The MD-CRS part II will be administered by the investigational center physician and video review for central-blinded reading. In this study, the MD-CRS part II will be scored only based on chorea.

Titration period (7 weeks): Patients who remain eligible for participation in the study will be randomized at the baseline visit (day 1) and instructed to take the first dose of blinded IMP the following morning 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 and CYP2D6 impairment status at baseline, as shown in Table 4 and Table 5. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer. At the baseline visit, a telephone for non-recording live video will be provided to the patient and caregiver. Patients and their caregiver will interact weekly with the

investigator/staff, either by telephone contact (with non-recording live video) or clinic visit from week 1 through week 7 of the titration period, in order to evaluate safety/tolerability and establish a dose of IMP that optimally reduces the severity of dyskinetic involuntary movements (clinically meaningful reduction in dyskinesia, as indicated by a reduction in the CGI-I) and is well tolerated. Safety/tolerability in-clinic evaluations during titration include assessment of vital signs, monitoring for adverse events and concomitant medications, 12-lead ECGs, identifying subjects at risk for suicide according to the C-SSRS questionnaire, 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. If a patient experiences a "clinically significant" adverse event attributable to the IMP, 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 dose will be established for the maintenance period. 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.

In-person (in-clinic) study visits will be scheduled for 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 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. The dose of the IMP should be increased on a weekly basis to reach a clinically meaningful reduction in dyskinesia, as indicated by a reduction in the CGI-I. The IMP dose should not be increased further if either of the following events occurs:

- the patient experiences a protocol-defined "clinically significant" adverse event (defined as an adverse event that is related to IMP 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 baseline.

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 IMP should not be increased further, but the patient should continue on that dose for the remainder of the titration period and throughout the maintenance period. If a patient experiences a "clinically significant" adverse event attributable to the IMP, 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.

Maintenance period (8 weeks): Patients will continue to receive their maintenance dose over the next 8 weeks, although a 1-time dose reduction (to the previous dose level for the remainder of the study) for adverse events is allowed. Patients will return to the clinic at weeks 9, 12, and 15 for assessments of efficacy and safety.

Washout period and follow-up: All patients will discontinue IMP at the week 15 visit and will return 1 week later for the end-of-study (EOS) visit. Patients who complete the study may be eligible to begin participation in the open-label safety extension Study TV50717-CNS-30081 at that time. At the week 16 visit, patients may choose to enter Study TV50717-CNS-30081 (on

that day) or up to 1 week later (2 weeks from the week 15 visit). Patients who complete treatment but choose not to participate in the open-label safety extension Study TV50717-CNS-30081 any time before week 17 of Study TV50717-CNS-30080 will be contacted for a safety evaluation call occurring 2 weeks after their last dose of IMP. Additional details for patients to enter Study TV50717-CNS-30081 are provided in the TV50717-CNS-30081 protocol.

When approximately 50 patients have completed the study (including follow-up), an independent Data Monitoring Committee (iDMC) will perform an unblinded non-binding interim analysis (IA) for futility based on centrally read MD-CRS part II total score.

An iDMC charter will be developed for the IA, and the procedures to ensure the integrity of the study will be provided in the charter.

At the time of informed consent, the parent/legally accepted representative will be counseled that, once randomized to treatment, patients are to remain in the study and complete all study procedures unless the choice is made to withdraw consent. Patients who withdraw from the study before completing the 15-week treatment period should have an early termination (ET) visit as soon as possible after the last dose of IMP. All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after ET; evaluations will be as described for week 17.

Patients who screen fail or terminate early from the study due to emergency circumstances (such as coronavirus disease 2019 [COVID-19]) may be allowed to re-screen/re-enter (respectively) the study at a later date, depending on the circumstances. Each case should be referred to the medical monitor and approved in advance.

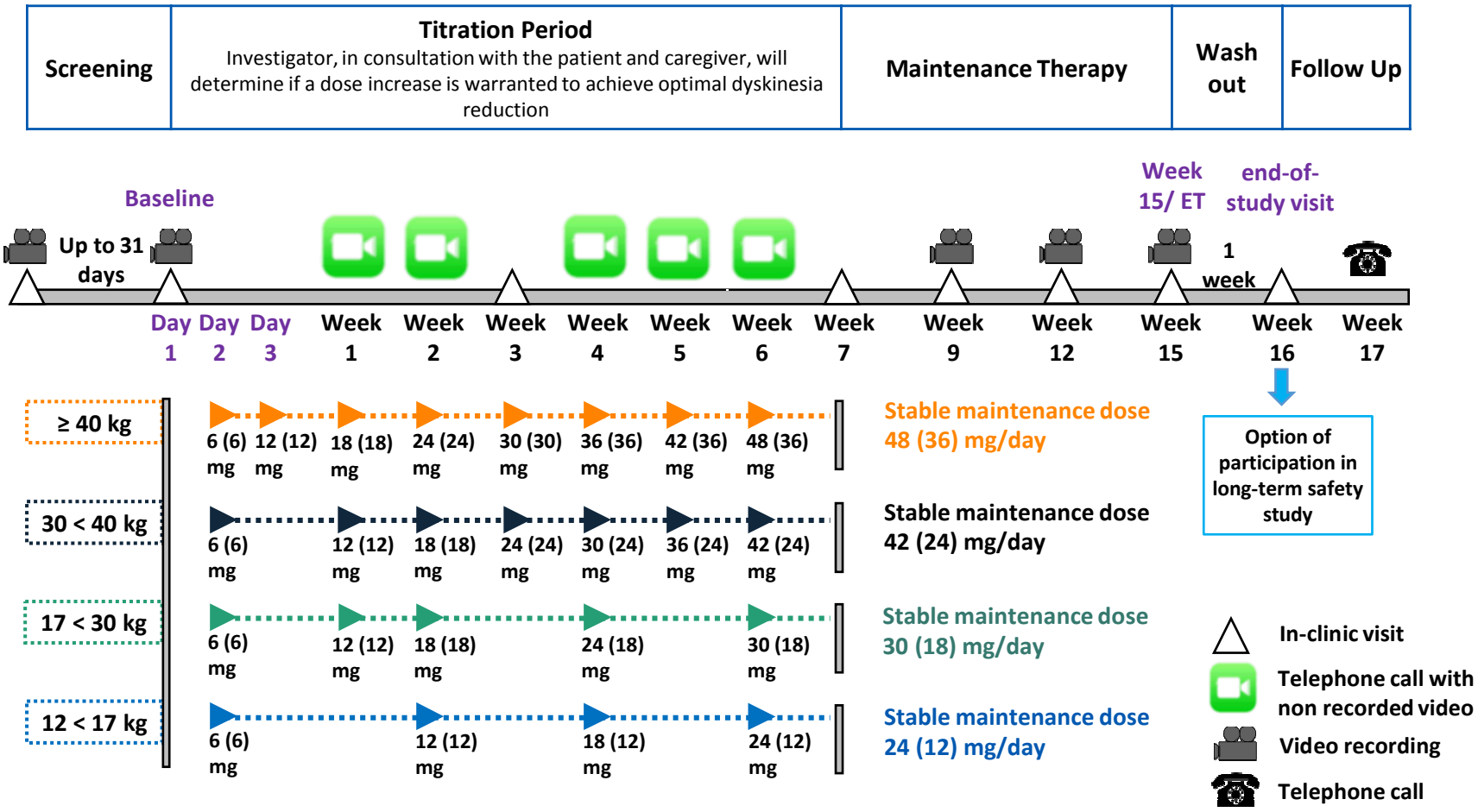
There is a separate protocol for the open-label safety extension Study TV50717-CNS-30081.

The end of study is defined as last visit of the last patient.

The study schematic diagram is presented in Figure 1.

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

Figure 1: Overall Study Schematic Diagram



AE=adverse event; CGI=Clinical Global Impression; CYP2D6=cytochrome P450 2D6; ET=early termination; max=maximum.
Note: If a patient is CYP2D6-impaired, the dose administered is indicated in parentheses. The dose of the IMP should be increased on a weekly basis 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 after remote or in-clinic visits.

3.2. Planned Number of Patients and Regions

Approximately 65 patients are planned to be randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 43 in the TEV-50717 group; approximately 22 in the placebo group) stratified by age at baseline (6 to <12 years; 12 through 18 years) and region (US; non-US).

Details on sample size are given in Section 9.1.

This study is planned to be conducted in approximately 60 investigational centers in North America, Asia, and Europe.

3.3. Justification for Study Design and Selection of Population

Currently, there is no approved treatment available for DCP. The available treatment options address some of the manifestations of DCP, which is hyperkinetic motor impairment due to a non-progressive disturbance of brain function that occurred in the developing fetal or infant brain, generally before the age of 2 years, and will therefore have a major debilitating impact on the ability of the child with CP to further develop motor skills. Therefore, 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). Diagnosis of DCP is based on the Surveillance of Cerebral Palsy in Europe criteria (Cans 2000).

Consequently, the placebo-controlled, double-blind study design (TEV-50717 versus placebo in a 2:1 ratio) was chosen for this Phase 3 study to determine whether treatment with study medication results in a statistically significant effect on dyskinetic involuntary movements of patients with DCP.

3.4. Stopping Rules for the Study

When approximately 50 patients have completed the study (including follow-up), an iDMC will perform an unblinded non-binding IA for futility based on the primary endpoint, the centrally read MD-CRS part II total score. Based on the results of the IA, the study may be stopped for futility.

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 should 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 in Table 3. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix C.

For COVID-19 updates, refer to Appendix M.

Table 3: Study Procedures and Assessments

	Screening	BL[a]	Titration							Maintenance			Follow-up		U
Study week[b]	**-31 days**	**Day 1**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**5 (Day 35)**	**6 (Day 42)**	**7 (Day 49)**	**9 (Day 63)**	**12 (Day 84)**	**15[c]/ ET[d] (Day 105)**	**16/EOS (7 days from week 15 visit)**	**17[e] (14 days from week 15 visit)**	
Visit window (days)		**0**	**+1**	**-1 and +3**	**±3 days from day 1/baseline and ≥5 days from last dose change**								**±2 days from week 15 visit**		
In-clinic visit	X[f]	X			X				X	X	X	X	X		X
Telephone contact[g]			X	X		X	X	X						X	X[h]
Evaluate/adjust IMP[i]			X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]						X
Informed consent/assent[k]	X														
Eligibility criteria	X	X													
Medical history and psychiatric history	X														
Demographics	X														
Vital signs and weight[l]	X	X[m]			X				X	X	X	X[m]	X		X
Physical examination	X	X										X			X[h]
Neurological examination	X	X										X			X[h]
Height	X											X			
12-lead ECG[n]	X				X				X			X	X[o]		X[h]
[redacted]												X[p]			X[q]
Chemistry/hematology/urinalysis	X											X	X[r]		X[h]
Urine drug screen	X				X					X		X	X		X[h]
CYP2D6 genotype[s]	X														
β-HCG test[t]	X	X			X				X		X	X	X		X[h]

	Screening	**BL**[a]	**Titration**							**Maintenance**			**Follow-up**		**U**
Study week[b]	**-31 days**	**Day 1**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**5 (Day 35)**	**6 (Day 42)**	**7 (Day 49)**	**9 (Day 63)**	**12 (Day 84)**	**15**[c]**/ ET**[d] **(Day 105)**	**16/EOS (7 days from week 15 visit)**	**17**[e] **(14 days from week 15 visit)**	
Visit window (days)		**0**	**+1**	**-1 and +3**	**±3 days from day 1/baseline and ≥5 days from last dose change**								**±2 days from week 15 visit**		
Randomization		X													
MD-CRS part I (physician rated, with video recording)[u]		X								X	X	X	X		X[h]
MD-CRS part I (centrally read, with video review)[u]		X								X	X	X	X		X[h]
MD-CRS part II (physician rated, with video recording)[u]	X	X								X	X	X	X		X[h]
MD-CRS part II (centrally read, with video review)[u]	X (EAB)	X								X	X	X	X		X[h]
CaGI-I[v]					X				X	X	X	X	X		X[h]
CGI-I (global, physician rated)[w]			X	X	X	X	X	X	X	X	X	X	X		X[h]
CGI-S (global, physician rated)	X	X			X				X	X	X	X	X		X[h]
PEDI-CAT (ADL, caregiver completed, content-balanced version)		X										X			X[h]
PedsQL (QoL, patient/caregiver)		X										X			X[h]
PGI-I (global, patient/caregiver)[v]					X				X	X	X	X	X		X[h]
UHDRS-TMC (centrally read)		X								X	X	X			X[h]
UHDRS-TMD (centrally read)		X								X	X	X			X[h]
UHDRS-TMS (physician rated)		X								X	X	X			X[h]

	Screening	**BL**[a]	**Titration**							**Maintenance**			**Follow-up**		**U**
Study week[b]	**-31 days**	**Day 1**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**5 (Day 35)**	**6 (Day 42)**	**7 (Day 49)**	**9 (Day 63)**	**12 (Day 84)**	**15**[c]**/ ET**[d] **(Day 105)**	**16/EOS (7 days from week 15 visit)**	**17**[e] **(14 days from week 15 visit)**	
Visit window (days)		**0**	**+1**	**-1 and +3**	**±3 days from day 1/baseline and ≥5 days from last dose change**								**±2 days from week 15 visit**		
Children's C-SSRS (Baseline/ Screening)[x]	X														
Children's C-SSRS (Since Last Visit)[x]		X			X				X	X	X	X	X		X[h]
ESRS subscales I and II	X	X			X				X	X	X	X	X		X[h]
CBCL[y]	X	X			X				X	X	X	X	X		X[h]
ESS	X	X			X				X	X	X	X	X		X[h]
Dispense IMP		X[z]			X[z]				X[aa]	X[aa]	X[aa]				X[h]
Collect IMP					X				X	X	X	X			X[h]
Assess IMP accountability/ compliance/supply[bb]			X[cc]	X[cc]	X[dd]	X[cc]	X[cc]	X[cc]	X	X	X	X			X[h]
Assess adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]	X[ee]
Contact RTSM	X				X				X	X	X	X			

[a] The BL visit will occur (day 1), and the first dose of the IMP will be taken the next morning (day 2).
[b] Assessment is to occur at the end of study week, unless stated otherwise.
[c] The date and time of the last dose of study medication before the week 15 visit should be reported to the investigator/staff by the patient or caregiver. The investigational center will document the date and time of the sample collection.
[d] For patients who withdraw prematurely, an ET visit should be conducted as soon as possible after the last dose of IMP. All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after ET visit; evaluations will be as described for week 17.
[e] This visit is a telephone contact for safety evaluation, required only for patients who will not roll over into the open-label safety extension study for TV50717-CNS-30081.
[f] The screening visit may be conducted over 2 separate visits at the discretion of the investigator.

[g] Telephone contacts at weeks 1, 2, 4, 5, and 6 will be conducted with non-recording live video. Telephone contact at week 17 is a phone contact only (ie, no live video streaming).

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

[i] 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.

[j] Dose adjustment will be made by the investigator after telephone contact with the patient and caregiver or in-clinic visit to evaluate dyskinesia reduction and adverse events. If the dose is escalated, the dose escalation will occur with the next morning's dose.

[k] [redacted]

[l] 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 or leg should be used each time vital signs are measured for a given patient).

[m] 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); for patients who find standing difficult or do not allow for a reliable BP and pulse measurement, alternative methods to collect orthostatic BP and pulse should be discussed with the medical monitor.

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

[o] Perform ECG if there was a significant abnormality at the ET visit.

[p] [redacted]

[q] [redacted]

[r] Patients with clinically significant laboratory abnormalities at week 15 will have those laboratory evaluations repeated at the week 16 visit.

[s] The patient's CYP2D6 genotype results will be provided to the RTSM, which drives each patient's dose regimen, and the patient's CYP2D6 genotype will remain blinded during the conduct of the study.

[t] For females who are postmenarchal or aged ≥12 years of childbearing potential. Serum test will be administered at screening and week 15, whereas a urine test will be administered at baseline and all other in-clinic visits where this test is administered.

[u] MD-CRS parts I and II assessments are done locally at the investigational center, by the investigator, and video recorded. An EAB will confirm, at the screening visit, that choreiform movement disorder is the predominant dyskinetic movement disorder and that DCP severity represented by an MD-CRS part II score is ≥10. The EAB will inform the local rater if their assessment is different than the local rater's assessment; however, it is the investigator who determines the subject's eligibility. All the subsequent MD-CRS ratings will be performed by the investigator and video recorded and then centrally read, in a blinded manner.

[v] CaGI-I and PGI-I are to be completed before all other investigator-rated scales during visits where CaGI-I and PGI-I are collected.

[w] During telephone contact, the CGI-I scale can only be done if non-recording video is available, allowing the investigator to complete the required assessment.

[x] The children's C-SSRS questionnaire will be presented to patients who have reached ≥12 years of age at screening or 11 years of age at screening but will turn 12 years of age during the study. Children 13 years of age and under must be interviewed in conjunction with the caregiver. For children over 13 years of age, parent/legally accepted representative involvement is strongly encouraged. Questions should be directed to the child, but the parent/legally accepted representative should be encouraged to add relevant information.

[y] A full CBCL assessment (Competence Scale [Parts I to VII] and a Syndrome Scale [behavioral items]) will be performed at screening and week 15/ET. The Syndrome Scale part of the CBCL assessment only will be performed at baseline and weeks 3, 7, 9, 12, and 16/EOS.

[z] IMP will be dispensed in the clinic. At the baseline visit, patients will receive IMP kits of increasing doses sufficient for 3 weeks. At the week 3 visit, 4 additional kits of increasing doses will be dispensed to cover the following 4 weeks until the end of the titration period at week 7. These supplies will allow the patient to maintain their titration scheme between clinic visits by way of remote caregiver/patient telephone contacts. Dose adjustments can be made up to and including the week 7 in-clinic visit. If an optimal dose is reached before then, the dose of IMP should not be increased any further, but the patient should continue on that same dose for the remainder of the titration period and throughout maintenance dosing. The investigational center will determine titration (ie, starting the next dose) for the patient by telephone. See Table 4 for baseline weight-based dosing titration. 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.

[aa] Patients will receive doses for 3 weeks (±3 days) of maintenance treatment.

[bb] 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.

[cc] The study staff needs to discuss the drug status during the telephone contacts to ensure that the patients have adequate tablets, inform the patients if they should titrate, and remind them to bring used and unused IMP bottles to the next in-clinic visit.

[dd] During the week 3 visit, the investigator or designee will make sure the patient receives the last treatment kit back so the patient can take the evening dose to complete the week 3 dosing for that day. Refer to the pharmacy manual for further details.

[ee] Caregivers and patients 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 if there is any change in current medications, including over-the-counter medications. Any new and/or any change in current medications should be reviewed with the investigator.

β-HCG=beta human chorionic gonadotropin; ADL=activities of daily living; BL=baseline visit; BP=blood pressure; CaGI-I=Caregiver Global Impression of Improvement; CBCL=Child Behavior Checklist (for ages 6-18); CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP2D6=cytochrome P450 2D6; DCP=dyskinesia in cerebral palsy; EAB=Enrollment Adjudication Board; ECG=electrocardiogram; EOS=end of study visit; ESRS=Extrapyramidal Symptom Rating Scale (subscales I and II); ESS =Epworth Sleepiness Scale (for children and adolescents); ET=early termination visit; [redacted]; IMP=investigational medicinal product; MD-CRS=Movement Disorder-Childhood Rating Scale; PEDI-CAT=Pediatric Evaluation Disability Inventory-Computer Adapted Test; PedsQL=Pediatric Quality of Life Inventory; PGI-I=Patient Global Impression of Improvement; [redacted]; QoL=quality of life; RTSM=Randomization and Trial Supply Management; 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.

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 related to concomitant medication, 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, which should remain constant throughout the course of the study.

4.1. Patient Inclusion Criteria

Patients may be randomized/enrolled in this study only if they meet all of the following criteria:

1. Patient is 6 through 18 years of age (inclusive) at baseline.
2. Patient weighs at least 26 pounds (12 kg) at baseline.
3. Patient has had CP symptoms since infancy (≤2 years), and CP is judged by the investigator to be of a non-progressive nature (Monbaliu et al 2017, Wimalasundera et al 2016).
4. Patient has a diagnosis of DCP according to the Surveillance of Cerebral Palsy in Europe criteria (Cans 2000).
5. Patient has an MD-CRS part II total score of ≥10 at the baseline visit, based on investigator scoring of chorea.
6. Patient's symptoms are causing functional problems determined by a CGI-S score of 4 or greater based on investigator scoring.
7. Choreiform is the predominant (ie, the main cause of impairment or distress) movement disorder as assessed at screening.
8. Patient is able to swallow study medication whole.
9. Patient and caregiver are willing to adhere to the medication regimen and to comply with all study procedures.
10. Patient is in good general health, as indicated by medical and psychiatric history, as well as physical and neurological examination.
11. 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.
12. For a patient who is a minor, the parent(s)/legally accepted representative(s) provide written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide their own written informed consent (in accordance with local regulations) and the legally acceptable representative will sign, if needed.

In this study, eligible patients are patients with dyskinetic CP who 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 assent/consent.

13. Caregivers provide written informed consent after being assigned the role by an adult patient, or if this role is delegated by the parent/legally accepted representative of a patient who is a minor.
14. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at baseline or are sterile. Definitions of sterile, premenarchal, and postmenarchal are given in Appendix F.
15. 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 screening) and for 30 days after the last dose of IMP. 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:

1. 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 other movement disorder that could impair the motor assessment in the MD-CRS part II.
   e. Patient has choreiform movement disorder that has not been consistent throughout the life of the patient.
2. Patient has clinically significant depression at screening or baseline.
   - Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening and anticipated to remain stable (dose and frequency) within the study duration.
3. Patient has a history of suicidal intent or related behaviors based on medical or psychiatric history or the C-SSRS within 2 years of screening:
   - 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
4. Patient has a history of a previous actual, interrupted, or aborted suicide attempt based on medical or psychiatric history or the C-SSRS.
5. Patient has a first-degree relative who has completed suicide.
6. Patient has received any of the following concomitant medications within the specified exclusionary windows of screening:

- Within 30 days: tetrabenazine, deutetrabenazine, or valbenazine
- Within 21 days: reserpine
- Within 14 days: levodopa, dopamine agonists, and MAOIs

7. Patient has received treatment with stem cells, deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation for treatment of abnormal movements or CP within 6 months of the screening visit, or the patient is not in a stable clinical condition.
8. Patient has recent surgical procedure 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.
9. Patient has a severe mental disability or an unstable or serious medical illness (eg, epilepsy) at screening or baseline that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.
10. Patient has a QT interval corrected for heart rate using Fridericia's formula (QTcF) value >450 msec on 12-lead ECG at screening.
11. Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, other cardiac arrhythmias, or uncompensated heart failure.
12. Patient has evidence of diminished hepatic function, as indicated by the following:
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × the upper limit of the normal range (ULN) at screening
    - Alkaline phosphatase (ALP) or total bilirubin >2 × ULN at screening
    - 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 the following clinical laboratory parameters must be approved for enrollment by the medical monitor: AST, ALT, ALP, and total bilirubin.
13. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5 × ULN at screening.
14. Patient has a known allergy to any of the components of the IMP.
15. Patient has participated in an investigational drug or device study and received IMP/intervention within 30 days or 5 drug half-lives of screening, whichever is longer.
16. Patient is pregnant or breastfeeding.
17. Patient has a history of or acknowledges alcohol or other substance abuse in the 12 months before screening.
18. Patient has a positive urine drug screen test result (with exception of medications listed in Table 10 of Appendix H). Any request to include a patient with a positive urine drug screen test result should be discussed with, and approved by, the medical monitor. Refer to Section 7.5.2.2 (urine drug screen) for more details.

4.3. Withdrawal Criteria and Procedures for the Patient

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

During the titration period, an optimal dose should be sought for each patient. Throughout the maintenance period, patients will continue to receive the optimal dose determined during titration. If a patient experiences a "clinically significant" adverse event attributable to the IMP, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible (Section 5.8). Each patient is free to withdraw from the study or discontinue from IMP at any time, without prejudice to their continued care, but every effort should be made to determine the reason for discontinuation.

Every effort should be made to ensure that patients comply with study visits and procedures, as detailed in the protocol. Patients must be withdrawn from the study if any of the following events occur:

1. Patient or parent(s)/legally acceptable representative withdraws consent or requests discontinuation from the IMP or withdrawal from the study for any reason.
2. Patient develops an illness that would interfere with his/her continued participation.
3. Patient is noncompliant with the study procedures and assessments or administration of IMPs in the opinion of the investigator.
4. Patient takes prohibited concomitant medications as defined in this protocol (see Appendix H).
5. Patient engages in alcohol or other substance abuse.
6. A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.
7. The sponsor requests withdrawal of the patient.
8. Patient experiences an adverse event or other medical condition that indicates to the investigator that continued participation is not in the best interest of the patient.
9. The patient experiences a serious adverse event or pregnancy, or in cases when the investigator deems it necessary to unblind the patient's IMP assignment to make treatment decisions.
10. Patient has evidence of diminished hepatic function based on the following liver function laboratory test results:
    a. AST or ALT >2.5 × ULN
    b. ALP or total bilirubin >2 × ULN
11. Patient develops Neuroleptic Malignant Syndrome (NMS)
12. If a post-baseline QTcF value >500 msec or change from screening >60 msec is found, the investigator should repeat the ECG assessment twice more and compare the average of these 3 post-screening QTcF values to the pre-treatment QTcF values at screening. The

IMP must be stopped for any confirmed post-baseline QTcF average value >500 msec or average increase from screening >60 msec.

13. In patients who experience signs of suicidal ideation or behavior (Section 7.9), the investigator should consult with the medical monitor to determine whether the patient should continue in the study.

In addition, a patient may be withdrawn from the study as described in Sections 3.4, 3.5, and 5.10 and Appendix C.

Because the statistical analysis of the primary endpoint of this study includes the assessment of randomness of missing data (Section 9.5.2.1), the most accurate as possible determination of the reason for ET is very important. Investigators should make every effort to obtain accurate information on patients in the case of withdrawal from the study or discontinuation from IMP. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study or discontinuation from IMP, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal from the study or discontinuation from IMP.

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.

If the reason for withdrawal from the study or discontinuation from IMP is an adverse event and/or clinically significant abnormal laboratory test result, monitoring will be continued as applicable (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 the IMP or study procedure is made). If a patient is withdrawn wholly or in part because of an adverse event, the specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the adverse events page and termination page of the CRF.

The patient will be monitored 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 the IMP or study procedure is made). The investigator must inform the clinical project physician/clinical leader as soon as possible of any patients who are being considered for withdrawal due to adverse event(s). Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that also include adverse events, the relevant page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that, in the opinion of the investigator, is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be “need to take a prohibited medication” and not the adverse event.

All assessments should be performed according to the protocol on the last day the patient takes IMP, or as soon as possible thereafter.

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 will not be replaced.

4.5. Rescreening

A patient who is screened but not enrolled (eg, because inclusion and exclusion criteria were not 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.

For COVID-19 updates, refer to Appendix M.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized 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 IMPs and matching placebo IMPs to the respective test IMPs. There is no reference 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. The IMP 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-, 12-, 15-, and 18-mg tablets by bottle and labeled according to applicable regulatory guidelines. Each bottle pack (20-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.

Additional details may be found in Table 6, the IB for TEV-50717, and the Prescribing Information for TEV-50717.

5.1.1.1. Starting Dose and Dose Levels

Test IMP 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 baseline are shown in Table 4. The maximum daily dose is determined by body weight at baseline and CYP2D6 impairment status (see Table 5). Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer. 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 IMP should not be increased further, but the patient should continue on that dose for the remainder of the titration period and throughout the maintenance period. If a patient experiences a “clinically significant” adverse event that is attributed to the IMP, 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 dose will be established for the maintenance period. If a patient experiences an adverse event during the maintenance period and the investigator believes a dose reduction is warranted, the dose may be reduced once for the remainder of the maintenance period.

TEV-50717 tablets (test IMP) are available in the following dose strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). Test IMP will be supplied in 20-count tablets per dose strength per bottle assembling 6, 12, 18, 24, 30, 36, 42, and 48 mg dose kit combinations. The placebo IMP tablets and packaging will match those for TEV-50717.

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.

IMP will be administered as follows:

- IMP should be swallowed whole. If the IMP is crushed or split, it should not be ingested; it should be replaced with a new tablet. The tablets will 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 will be based on body weight at the baseline visit and CYP2D6 impairment status, as shown in Table 4 and Table 5, respectively.
- If there is only a single dose of IMP per day, the dose should be taken in the morning. However, patients experiencing somnolence while taking the 6-mg dose in the morning may switch to taking it as an evening dose for the rest of the days up to day 14.
- The starting dose of 6 mg will be administered in the morning on day 2 and for the remainder of the first week. Patients in the highest body weight group (≥40 kg/88 lbs) will start an evening administration from day 3 and for the remainder of the first week. 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.
- 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.
- During the week 3 visit, the investigator or designee will make sure the patient receives the last treatment kit back so the patient can take 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 IMP should be adjusted according to Table 4 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 telephone or in-clinic visit.

Table 4: Maximum Daily Dose of IMP During the Titration Period by Week and Weight Category at Baseline

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[d]	18 mg[d]	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 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 3 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, or those who are poor CYP2D6 metabolizers, 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 5).
CYP2D6=cytochrome P450 2D6; IMP=investigational medicinal product.

Table 5: Maximum Daily Dose of IMP 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; IMP=investigational medicinal product.
Note: Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer. Strong CYP2D6 inhibitors include paroxetine, fluoxetine, and bupropion.

5.1.2. Placebo Investigational Medicinal Product

Placebo tablets match TEV-50717 tablets. Additional details may be found in Table 6.

Table 6: Investigational Medicinal Products Used in the Study

IMP Name	TEV-50717 Test IMP	Placebo IMP
Company-assigned number	TEV-50717 (SD-809, AUSTEDO®, deutetrabenazine)	Not applicable
Formulation	Modified release solid oral dosage form (tablet with film coating)	Modified release solid oral dosage form (tablet with film coating)
Unit dose strength(s)/Dosage level(s)	TEV-50717 tablets are available in the following dose strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). Test IMP will be supplied in 20-count tablets per dose strength per bottle.	Not applicable
Route of administration	Oral	Oral
Packaging	Test IMP will be provided in bottles.	Placebo 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 4745 Wiley Post Way Salt Lake City, UT 84116	Norwich Pharmaceuticals Inc., New York, United States (Referenced as NPI or Norwich) 6826 State Highway 12 Norwich, NY 13815 Anesta LLC 4745 Wiley Post Way Salt Lake City, UT 84116
Storage conditions[a]	Stored at controlled room temperature, 20°C-25°C (68°F-77°F)	Stored at controlled room temperature, 20°C-25°C (68°F-77°F)

[a] For additional information related to the IMP storage condition, refer to Section 11 of the Pharmacy Manual.
IMP=investigational medicinal product.

5.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products

5.2.1. Storage and Security

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

The IMPs (TEV-50717 and placebo IMP) must be stored at a controlled room temperature, 20ºC to 25ºC (68ºF to 77ºF), in a securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff. For additional information related to the IMP storage condition, refer to Section 11 of the Pharmacy Manual.

5.2.2. Labeling

Supplies of IMPs will be labeled according to the current International Council for Harmonisation 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 IMP shipment will include a packing slip listing the contents of the shipment and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMPs 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 IMPs, and only authorized staff at the investigational center may supply or administer IMPs. All IMPs 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 the IMP 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 IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

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 (☋+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 TV50717-CNS-30046 Phase 2/3 and TV50717-CNS-30060 Phase 3 studies of TEV-50717 in TS.

5.3.2. Justification for Use of Placebo Investigational Medicinal Product

A standard placebo-controlled, double-blind study design (TEV-50717 versus placebo in a 2:1 ratio) was chosen to determine whether TEV-50717 treatment results in a statistically significant effect on the motor system of patients with CP. As CP is not a progressive neurological disorder, and available treatments are for symptomatic control, the use of placebo is justified in a short-term study where safety is carefully monitored. Moreover, a placebo control is ideal for characterizing the efficacy and safety of an experimental agent in a new study population.

5.4. Treatment after the End of the Study

All patients will discontinue IMP at the week 15 visit and will return 1 week later for the EOS visit. [redacted] Patients will not receive the evening IMP dose on this day.

Patients who complete the study may be eligible to begin participation in the open-label safety extension Study TV50717-CNS-30081. At the week 16 visit, patients may choose to enter Study TV50717-CNS-30081 (on that day) or up to 1 week later (2 weeks from the week 15 visit). Patients who complete treatment but choose not to participate in the open-label safety extension Study TV50717-CNS-30081 before week 17 of Study TV50717-CNS-30080 will be contacted for a safety evaluation call occurring 2 weeks after their last dose of IMP. Additional details for patients to enter Study TV50717-CNS-30081 are provided in the TV50717-CNS-30081 protocol.

Note: Patients can also roll over to the extension study within 2 to 4 weeks after the week 15 visit but will be required to complete additional scales and tests as part of Study TV50717-CNS-30081.

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 baseline 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 IMP dosing can be made. The addition of a strong CYP2D6 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 non-approved drugs (per protocol) 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 IMP, and for 14 days after the last dose.

5.6. Prior and Concomitant Medication

Any prior or concomitant medication a patient has had within 3 months prior to baseline and up to the end of study, including follow-up, will be recorded on the CRF. Generic or trade name, indication, dose, and start and end dates of the administered medication will be recorded. The sponsor will encode all medication according to the World Health Organization drug dictionary.

At each clinic visit after the screening visit, the investigator will ask patients and/or caregiver whether the patient has taken any medications (other than IMP), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit. Caregivers and patients 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 if there is any change in current medications, including over-the-counter medications. Any prescribed new and/or any change in current 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 QT prolongation or that is a known strong CYP inhibitor. Allowed strong CYP inhibitors at baseline are shown in Appendix H, Table 10. The addition of a strong CYP inhibitor is prohibited during the study.

Prohibited medications that are associated with QT prolongation are listed in Appendix H, Table 11.

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 IMP. A check of compliance with IMP intake will be performed during each in-clinic visit after the used IMP has been returned, and IMP accountability records will be completed. At week 3, IMP administration compliance can be calculated only for weeks 1 and 2, as the last kit at week 3 is returned to the patient so that the patient can complete the week 3 dosing for that evening.

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 intake (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 IMP will be assessed as required (Section 5.1).

5.8. Temporary Discontinuation of Investigational Medicinal Product

Refer to Table 3 for data to be collected at the time of IMP 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 IMP, the investigator will first determine if a dose reduction (to the previous dose level) or suspension is necessary and possible. Dose adjustments should be made based on all available information, including the patient’s and parent’s/caregiver’s reports of adverse events and motor function improvement, the clinical assessment of safety and efficacy by the investigator, and information from rating scales. **If more than 1 dose reduction is required for an adverse event, the medical monitor should be notified.** Suspension of IMP treatment for up to 1 week, if warranted, is allowed. If the patient restarts IMP within 7 days of suspension, the full dose of IMP may be resumed without titration at the same dose level or 1 dose lower (last tolerated dose). Suspension of IMP treatment for adverse events must be reviewed with the medical monitor before IMP 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 reduction or suspension is allowed once during the titration period and once during the maintenance period. Patients who restart IMP treatment will remain at the current dose throughout that period with no further dose changes 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 7 days after the change.

If a dose suspension occurs before a scheduled clinic visit, an unscheduled visit should be scheduled as soon as possible so that efficacy evaluations can be performed at least 7 days after the change.

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.

If a patient's serum potassium or magnesium level falls below the lower limit of normal, IMP 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. IMP treatment may only be restarted once serum potassium and/or magnesium levels have normalized.

Patients who restart IMP treatment will follow the visit schedule as outlined in Table 3. Patients who withdraw from the study will proceed as described in Section 4.3.

5.9. Randomization and Blinding

This is a double-blind study. Patients will be randomized to either TEV-50717 or matching placebo in a 2:1 ratio using Randomization and Trial Supply Management (RTSM). Patients will be stratified by age at baseline (6 to <12 years; 12 through 18 years, inclusive) and region (US; non-US). Patients and investigators will remain blinded to treatment assignment during the study. In addition, the sponsor's clinical personnel and all vendors (with the exception of the sponsor's clinical supply chain staff and RTSM vendor) will be blinded to the IMP identity until the database has been locked for analysis and the treatment assignments are revealed.

The iDMC will perform an unblinded non-binding IA for futility and will monitor safety throughout the study based on unblinded data. An iDMC charter will be developed for the interim analyses, and the procedures to ensure the integrity of the study will be provided in the charter (see Section 5.10.3 for more details).

In the event of an emergency, it will be possible to determine to which treatment group and dose the patient has been allocated by accessing the RTSM system. All investigational centers will be provided with details of how to access the system for code breaking at the start of the study. The medical monitor or equivalent should be notified following unblinding. Any unblinding of the IMP performed by the investigator must be recorded in the source documents.

Patients re-entering the study will be manually assigned to their initial treatment group by the RTSM unblinded vendor. Blinding will be maintained for the patient, investigator, and sponsor as described above; the only information that will be available is that the patient was assigned to the same treatment group previously.

The randomization list will be assigned to the relevant treatment groups through a qualified service provider (eg, via an RTSM system). The generation of the randomization list and management of the RTSM system will be done by a qualified service provider under the oversight of the responsible function at Teva.

5.10. Maintenance of Randomization and Blinding

5.10.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of analysis (after the end of study or at the IA), after receiving unblinding request from a Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant standard operating procedure. For the IA and iDMC closed sessions, the codes will be provided to an independent statistician who will perform the IA.

5.10.2. Blinding and Unblinding

For information about personnel who may be aware of IMP assignments, see Section 5.9. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events.

In case of a serious adverse event, pregnancy, or in cases when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations, through specialized access in the RTSM system. Breaking of the treatment code may always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified that the code was broken, but the patient treatment assignment should not be revealed to the sponsor.

When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded on the CRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP should not be recorded in any study documents or source document.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study and analysis and reporting of the data.

5.10.3. Independent Data Monitoring Committee

There will be an iDMC in this study.

When approximately 50 patients have completed the study (including follow-up), the iDMC will perform an unblinded non-binding IA for futility based on centrally read MD-CRS part II total score.

Details on how the iDMC chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study are described in the iDMC charter. The iDMC charter will be developed for the IA, and the procedures to ensure the integrity of the study will be provided in the charter. The sponsor will work closely with the iDMC to provide the necessary safety and efficacy data for review. In addition, results of the IA will be communicated to the sponsor as outlined in the iDMC charter.

Details are given in Appendix B.

5.11. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 40 mL (at maximum), as detailed 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 PGI-I. 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-30080 RECLAIM-DCP: Order of scales administration/completion document). At all relevant visits where collected, PGI-I and CaGI-I are to be completed before all other investigator-rated 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.

For COVID-19 updates, refer to Appendix M.

6.1. Primary Efficacy Measure

The primary efficacy measure is centrally read MD-CRS part II total score, which 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).

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 and 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. 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).

The MD-CRS part II will be administered by the investigational center physician, or other appropriately trained study team member, and video-recorded at screening, baseline, week 9, week 12, week 15/ET, and week 16/EOS visits.

The MD-CRS has been updated to version 2 with changes to the scoring language. This version should be used when available. However, a patient will complete all study visits using the same version.

Assessment of MD-CRS part II items will be based solely on chorea in this study and performed as follows:

- Local assessment (all time points): the investigational center physician will administer the MD-CRS part II and complete the assessment of item scores. Note: the physicians will receive training on MD-CRS scoring prior to the study.
- EAB review (screening): EAB will review the MD-CRS part II at the screening visit to confirm that dyskinesia severity is aligned with the protocol criteria for inclusion into the study. The review will include determination of the predominant dyskinesia type and scoring of MD-CRS part II items. The EAB will inform the site prior to the baseline visit if there are any discrepancies between the local and central assessments, and offer to discuss with the investigator. Ultimately, it is the investigator who determines the patient's eligibility. EAB assessment of screening MD-CRS part II total score will not be included in the statistical analysis.
- Central reading (baseline, week 9, week 12, week 15/ET, and week 16/EOS): Video review of MD-CRS part II will be assessed periodically 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, who are also the EAB members, will not be disclosed to the investigational site. Central reading details will be provided in a separate charter.

The primary efficacy endpoint is the change from baseline to week 15 in the MD-CRS part II total score (TEV-50717 versus placebo), assessed by central reading.

6.2. Key Secondary Efficacy Measures

6.2.1. Movement Disorder-Childhood Rating Scale Part I Total Score

The MD-CRS part I evaluates 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 I will be administered at baseline, week 9, week 12, week 15/ET, and week 16/EOS visits. The MD-CRS part I will be administered by the investigational center physician and video recorded for central blinded review. 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.

6.2.2. 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 3). 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);

2=much improved;

3=minimally improved;

4=no change from baseline (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 3, week 7, week 9, week 12, week 15/ET, and week 16/EOS visits.

6.2.3. Clinical Global Impression of Improvement Scale

Each time the patient is seen during the treatment period (ie, 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 baseline visit (Busner and Targum 2007). The CGI-S score obtained at the baseline visit (see Section 6.3.9) serves as a good basis for making this assessment. The CGI-I is a ClinRO that uses a 7-point Likert scale that allows the clinician to compare the patient's condition at the visit to the baseline condition as follows (with anchor points for choosing the most appropriate improvement level):

1=very much improved since the initiation of treatment (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 baseline (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 (severe exacerbation of symptoms and loss of functioning).

The CGI-I administered at the in-clinic visits (week 3, week 7, week 9, week 12, week 15/ET, and week 16/EOS) will be included in the analysis of the key secondary endpoint. Patients will also be assessed for CGI-I during telephone contacts (with non-recording live video) at week 1, week 2, week 4, week 5, and week 6.

6.2.4. Unified Huntington's Disease Rating Scale-Total Maximal Chorea

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).

A central reading of the UHDRS-TMC will be performed at baseline and at weeks 9, 12, 15/ET, and 16/EOS 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.

6.2.5. Unified Huntington's Disease Rating Scale-Total Maximal Dystonia

The UHDRS-Total Maximal Dystonia (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). When rating dystonia (question #11), buccal-oral-lingual and facial dystonia (blepharospasm, jaw opening and closing) should be included in the assessment of the truncal region.

A central reading of the UHDRS-TMD will be performed at baseline and at weeks 9, 12, 15/ET, and 16/EOS 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.

6.3. Other Efficacy Measures

6.3.1. Movement Disorder-Childhood Rating Scale Part I and Part II Total Scores

The MD-CRS part I and part II total scores will be evaluated by the investigator at baseline, week 9, week 12, week 15/ET, and week 16/EOS visits. See Section 6.1 and Section 6.2.1 for description of these rating scales.

6.3.2. Movement Disorder-Childhood Rating Scale Global Index

The MD-CRS Global Index is a global measure of the MD-CRS that consolidates the information from parts I and II using the method of weighted means of the 2 normalized indexes obtained from each part (Battini et al 2008). The minimum score is 0 and the maximum score is 1.

6.3.3. 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 Total Motor Score assessment of the UHDRS (UHDRS-TMS) comprises 15 items and assesses eye movements, speech, alternating hand movements, dystonia, chorea, and gait. The UHDRS-TMS is calculated as the sum of the 31 motor assessments; each of which range between 0 to 4. The minimum score is 0 (absent) and the maximum score is 124 (worst) (Huntington Study Group 1996).

The protocol refers to UHDRS-TMS 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-TMS.

The UHDRS-TMS is administered at baseline, week 9, week 12, and week 15/ET visits, and will be rated by the investigator.

6.3.4. Unified Huntington's Disease Rating Scale-Total Maximal Chorea

The UHDRS-TMC is administered at baseline, week 9, week 12, and week 15/ET visits, and will be rated by the investigator.

6.3.5. Unified Huntington's Disease Rating Scale-Total Maximal Dystonia

The UHDRS-TMD is administered at baseline, week 9, week 12, and week 15/ET visits, and will be rated by the investigator.

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

The Pediatric Evaluation of Disability Inventory Computer Adaptive Test (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 baseline and at week 15/ET visits.

6.3.7. Pediatric Quality of Life Inventory, Cerebral Palsy Module

The Pediatric Quality of Life Inventory (PedsQL™) is a health-related quality-of-life instrument that consists of a well-validated generic core measure and some condition and disease-specific modules (Varni et al 2006). The 35-item PedsQL 3.0 CP module encompasses 7 scales: (1) Daily

Activities (9 items); (2) School Activities (4 items); (3) Movement and Balance (5 items); (4) Pain and Hurt (4 items); (5) Fatigue (4 items); (6) Eating Activities (5 items); and (7) Speech and Communication (4 items).

The scales comprise parallel child self-report and parent proxy-report formats. For children ages 6 and 7 years and 8 to 12 years, a child self-report and a parent proxy report are completed. The parent proxy report assesses parents' perceptions of their child's health-related quality of life (QoL). For children ages 13 to 18 years, no parent proxy report is required. The instructions ask how much of a problem each item has been during the past 1 month. A 5-point response scale is utilized across child self-report and parent proxy report as follows:

0=never a problem;
1=almost never a problem;
2=sometimes a problem;
3=often a problem;
4=almost always a problem.

The PedsQL is administered at baseline and at week 15/ET visits. Input from the caregiver is permitted.

6.3.8. Patient Global Impression of Improvement Scale

The Patient Global Impression of Improvement (PGI-I) is single item questionnaire to assess the patient's impression of improvement in dyskinesia symptoms after initiating therapy. The scale is a patient-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 PGI-I is to be completed before all other investigator-rated scales during visits where PGI-I is collected (Table 3). The patient has to select the 1 response from the visual response options ("emojis") that gives the most accurate description of his/her state of health and overall status:

1=much improved (since the initiation of treatment);

2=somewhat improved;

3=no change;

4=somewhat worse;

5=much worse (since the initiation of treatment).

The PGI-I is administered at week 3, week 7, week 9, week 12, week 15/ET, and week 16/EOS visits. Input from the caregiver is permitted.

6.3.9. 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 is administered at screening, baseline, week 3, week 7, week 9, week 12, week 15/ET, and week 16/EOS visits. Input from the caregiver is permitted.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel and will include the evaluation of adverse events (and the number of patients who withdraw from the study due to adverse events), vital signs, laboratory tests (hematology, chemistry, and urinalysis), ECG measurements, CBCL, ESRS, ESS, and the children's C-SSRS. The investigator should review all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly.

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 that 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 the screening visit 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 IMP or up to baseline/day 1 in the open-label extension Study TV50717-CNS-30081 (whichever comes first) or 2 weeks after the ET visit for patients who terminate early from the study.

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 the IMP. 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 periods.

At each contact with the patient, the investigator or designee must question the patient and/or parent(s)/caregiver (as applicable) 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 the IMP or study procedure is made. Adverse events of patients rolling over to the open-label extension Study TV50717-CNS-30081 will continue to be monitored as part of the open-label extension study.

To enable the assessment of the potential relationship of an adverse event and plasma concentration of IMP and metabolites, blood samples will be collected based on the scenarios described in Table 9.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP, 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 IMP 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 one 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 is characterized in Table 7 as follows:

Table 7: 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: 1. It does not follow a reasonable temporal sequence from the administration of the IMP. 2. 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. 3. It does not follow a known pattern of response to the IMP. 4. 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: 1. It follows a reasonable temporal sequence from administration of the IMP. 2. 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. 3. 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. 4. 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 preexisting 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:

- ALT or AST increase of >3× ULN
- total bilirubin increase of >2× ULN
- absence of initial findings of cholestasis (ie, no substantial increase of 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 GPSP will determine the expectedness for all serious adverse events.

For the purpose of 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 the IMP, 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); 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 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 the IMP, study procedures, and to underlying diseases.

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 form/Extensible Markup Language 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.

Blinding will be maintained for all study personnel. Therefore, in case of an SUSAR, only the LSO/CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the IMP 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). 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.

7.2.1. Children's Columbia-Suicide Severity Rating Scale

The children's C-SSRS Baseline/Screening scale assesses past and current suicidal ideation and behaviors to determine suicide risk and is administered at screening. The children's C-SSRS Since Last Visit scale is administered at baseline, weeks 3, 7, 9, 12, 15/ET, and 16. The children's C-SSRS questionnaire will be presented to patients ≥12 years of age at screening or 11 years of age at screening but will turn 12 years of age during the study. Children 13 years of age and under must be interviewed in conjunction with the caregiver as appropriate or defined by the scale. For children over 13 years of age, parent/legally accepted representative involvement is strongly encouraged. Questions should be directed to the child, but the caregiver parent/legally accepted representative 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 baseline, compared to the worst (highest) category during the treatment period, will be presented.

7.2.2. Child Behavior Checklist (for Ages 6-18)

The CBCL assesses behavioral and emotional status in children ages 6 through 18 years of age as reported by the caregiver (Achenbach and Ruffle 2000; Achenbach 2005). The full CBCL has two 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 113 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 and Syndrome Scales) will be completed at screening and at week 15/ET. Only the CBCL Syndrome scale will be completed at baseline, weeks 3, 7, 9, 12, and 16/EOS.

7.2.3. 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 screening; baseline; and weeks 3, 7, 9, 12, 15/ET, and 16/EOS.

The 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: 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.

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

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. In 2017, Janssen et al 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.

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 is administered at screening; baseline; and weeks 3, 7, 9, 12, 15/ET, and 16/EOS. The ESS asks respondents to rate, on a 4-point Likert scale (0–3), their usual chances of dozing off or falling asleep in different situations or activities that most people engage in as part of their daily lives. The total ESS score is the sum of 8 item scores and can range between 0 and 24 with 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 IMP.

All pregnancies of female patients participating in the study that occur during the study or within 14 days after the end of study are to be reported immediately 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).

The investigator is not required to report patients who are found to be pregnant between screening and baseline, provided no IMP was given. 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.

Note: Female partners' pregnancies of male participants are not required to be proactively monitored.

If the pregnancy in the female patient participating in the study does not continue to term, one 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 Products

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

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 (whether the test IMP, or placebo IMP), 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 the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

Table 8: 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	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, and urinalysis) will be performed at screening, week 15, and week 16, as detailed in Table 3. Clinical laboratory tests will be performed using the central laboratory**.** Specific laboratory tests to be performed are provided in Table 8. Laboratory tests performed at screening may be repeated to determine patient eligibility.

7.5.2. Other Clinical Laboratory Tests

7.5.2.1. Beta-Human Chorionic Gonadotropin Tests

β-HCG tests in urine will be performed for all female patients aged 12 years or older of childbearing potential at baseline and other in-clinic visits as detailed in Table 3. The β-HCG tests in serum will be performed for all female patients aged 12 years or older of childbearing potential at screening and week 15 and if clinically indicated.

For COVID-19 updates, refer to Appendix M.

7.5.2.2. Urine Drug Screen

A urine drug screen will be performed at the time points specified in Table 3. A urine drug screen performed at screening may be repeated to determine patient eligibility.

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, or if the investigator considers that additional testing is needed, an alternative matrix (eg, serum) may be considered acceptable. Such tests may be performed locally. 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 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 or 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) and if the dosing has been stable for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. Such cases should be discussed with the medical monitor. Patients who either are using these medications or have a positive drug screen for these substances or derivatives should be submitted to the medical monitor for consideration of participation in this study. Patients with a substance use disorder are excluded from this clinical trial. However, if per the investigator's judgment, a patient does not meet the criteria for substance use disorder, a positive drug screen result 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.

For COVID-19 updates, refer to Appendix M.

7.6. 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 3.

Weight must be measured with shoes and outerwear off.

Any new physical examination finding (ie, since the screening visit) 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.

7.7. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, body temperature, and pulse) will be measured at the time points detailed in Table 3. 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 or 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 patients who find standing difficult or do not allow for a reliable blood pressure and pulse measurement, alternative methods to collect orthostatic blood pressure and pulse should be discussed with the medical monitor. 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.

7.8. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 3. All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.

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 30 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 a central diagnostic center will be interpreting 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 (except at the screening visit) 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 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.

Note: Abnormal ECG results at week 3 and week 7 or at an unscheduled visit may result in patient withdrawal from the study as detailed in Section 4.3.

7.9. 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.

Families and 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.

Baseline 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.

7.10. Assessment of Depression

Families and 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, 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.

7.11. 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 3. Any neurological examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with the baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

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 (other than TEV-50717) or if there is any change in current medications, including over-the-counter medications. Any new prescribed/administered medication and/or any change in current 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 can be submitted to the medical monitor for consideration of participation in this study. Patients with a substance use disorder 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.

Medications that are allowed, provided that conditions outlined in the table are met, are shown in Appendix H, Table 10. 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 and should be discussed with the medical monitor. If the wellbeing of the patient and the urgency of the clinical decision do not allow discussion with the medical monitor prior to the medication change, the investigator should notify the medical monitor in a timely manner following this decision.

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 prolongation or that is a known strong CYP2D6 inhibitor. Prohibited medications that are associated with QT prolongation are listed in Appendix H, Table 11.

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. In addition, the iDMC will perform the unblinded IA and take part in safety monitoring throughout the study.

Methods and time points of assessing safety data are discussed in Section 3.4. Procedures for recording safety data are discussed in Appendix K, and methods of analyses are discussed in Section 9.8.

8. ASSESSMENT OF PHARMACOKINETICS/ PHARMACODYNAMICS AND PHARMACOGENETICS

8.1. Pharmacokinetic Assessment

[redacted]

Table 9: Blood Sampling Scenarios

Scenario	Action
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

8.2. Assessment of Exploratory Biomarkers

[redacted]

8.3. Pharmacogenetics

8.3.1. CYP2D6 Genotyping/Pharmacogenetics

At the screening visit, a mandatory blood sample (3.0 to 5.0 mL) will be obtained for analysis of CYP2D6 genotype from all patients in the study at the time point detailed in Table 3. The CYP2D6 genotype results will be provided to the RTSM, which drives each patient's dose regimen, and the patient's genotype for CYP2D6 will remain blinded during the conduct of the study.

[redacted]

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 (SAP). After finalization of the SAP, any additional analyses or changes to analyses that may be required will be fully disclosed in the CSR.

For COVID-19 updates, refer to Appendix M.

9.1. Sample Size and Power Considerations

The initial sample size estimation of approximately 185 patients randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 124 in the TEV-50717 group; approximately 61 in the placebo group) is the sample size required to obtain a statistically significant result in the primary analysis based on a 1-sided test for mean difference at a significance level of α=0.025 with a power of approximately 90%, assuming a mean difference of 1.8 and a standard deviation (SD) of 3.5 in each treatment group.

At the time of writing Amendment 05, the initially planned sample size has been reduced to approximately 65 patients randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 43 in the TEV-50717 group; approximately 22 in the placebo group).

The initial assumptions regarding the mean difference and SD are based on the change from baseline to month 6 in patients treated with trihexyphenidyl reported by Battini et al (2014), assuming an effect size of 55% for TEV-50717 versus placebo. The effect size of 55% was assumed based on the observed effect sizes of TEV-50717 in the pivotal studies in HD and TD. In the current study, these assumptions correspond to a mean difference of 2.0 in MD-CRS part II total score and an SD of 3.5 in each treatment group.

The rate of missing not at random (MNAR) data for the primary analysis is expected to be 10%. MNAR data will be imputed in a conservative manner as if they were obtained from patients in the placebo treatment group, regardless of the actual treatment group. As a result, the mean difference is expected to be reduced from 2.0 to 1.8 in the primary analysis. The impact of the missing data imputation on the SD is negligible.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients.

In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

For patients who discontinue the study and re-enter it (repeating the study from baseline), only the data from the repeated participation will be included in the ITT analysis set.

9.2.2. Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including all randomized patients with at least 1 post-baseline centrally read MD-CRS part II assessment.

In the mITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

9.2.3. Safety Analysis Set

The safety analysis set will include all randomized patients who receive at least 1 dose of IMP.

In the safety analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

Rules for assignment of treatment in case of mixed actual treatments will be provided in the SAP.

Rules for handling safety data for patients who discontinue the study and re-enter it will be provided in the SAP.

9.2.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the mITT analysis set including only patients who meet the following criteria:

- compliant with study medication (80% to 105%)
- complete the study without any major protocol deviations that may impact efficacy
- centrally read baseline MD-CRS part II total score of ≥10

Rules for excluding patients from the PP analysis set will be provided in the SAP. Evaluation of exclusion from the PP analysis set will be discussed on a case-by-case basis and documented prior to database lock and unblinding of the study for final analysis.

9.3. Data Handling Conventions

9.3.1. Handling Withdrawals and Missing Data

For this study design and population, it is unlikely that patients who withdraw from IMP will be willing to attend the remaining scheduled study visits and, in particular, the week 15 visit. Therefore, patients will not be required to return to the clinic at week 15 for efficacy evaluations, and the primary analysis will be based on a multiple imputation method for missing data.

For efficacy analysis, missing data will be classified as missing at random (MAR) and MNAR. The following cases will be considered as MNAR:

- early terminations related to tolerability
- treatment-related adverse events
- early terminations related to lack of efficacy

The following cases will be considered as MAR:

- intermittent missing data
- early termination for patients who are lost to follow-up
- early terminations due to COVID-19

For all other cases, and for cases classified as above, classification as MAR/MNAR will be done/revisited in a blinded manner on a case-by-case basis prior to the IA for futility and prior to database lock for final analysis.

Multiple imputation methods will be used in the primary and secondary efficacy analyses. See Section 9.5 for details.

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 by treatment group and for all patients.

9.4.1. Patient Disposition

Data from patients screened; patients screened but not randomized (and reason not randomized); patients who are randomized; patients randomized but not treated; patients re-randomized; patients in the ITT, mITT, safety, and PP analysis sets; patients who complete the treatment period; patients who complete the EOS visit; 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, including medical and psychiatric history, prior medications and therapies, and ECG findings, will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics. 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. Efficacy Analysis

9.5.1. Primary Estimand

The primary estimand is the difference in means between TEV-50717 and placebo in the target patient population for the change from baseline to week 15 in centrally read MD-CRS part II total score, regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events.

The primary estimand assesses the effectiveness in the reduction of choreiform movements in patients with DCP with predominant choreiform movement disorder, evaluated by the central reviewers, focusing on the causal effects attributable to the IMP.

The target patient population for this study is patients with DCP with predominant choreiform movement disorder and severity of DCP represented by the following:

a. total score of ≥10 in centrally read MD-CRS part II items at baseline, and
b. CGI-S ≥4 at baseline.

This population is expected to have the sensitivity to demonstrate clinically meaningful improvement following treatment with TEV-50717.

Due to practical reasons, it is not possible to obtain a central reading of MD-CRS part II items at the time of the baseline visit prior to randomization; therefore, inclusion of the subject to the study is based on investigator scoring of MD-CRS part II items at baseline (Section 9.2.2).

9.5.2. Primary Endpoint

The primary efficacy endpoint is the change from baseline to week 15 in the MD-CRS part II total score (movement disorder severity, centrally read) (TEV-50717 versus placebo).

9.5.2.1. Primary Efficacy Analysis

The primary analysis will be a mixed-model, repeated-measures with the change in MD-CRS part II total score as the dependent variable. The model will include fixed effects for treatment group, week (3 levels: weeks 9, 12, and 15), and treatment group by week interaction. The baseline MD-CRS part II total score, age group at baseline (2 levels: 6 to <12 years; 12 through 18 years, inclusive), and region (US; non-US) will be included as covariates. The unstructured covariance model will be used.

Missing data will be classified as MAR and MNAR, as described in Section 9.3.1. The MAR/MNAR multiple imputation method will be applied in the primary analysis, where MNAR data will be imputed using the jump-to-reference method, and MAR data will be imputed based on the randomized treatment group. The resulting complete, imputed datasets will each be analyzed using the analysis model described above, and the resulting statistics combined using methodology presented by Rubin (1987) and Little and Rubin (2002).

The difference in least squares (LS) mean of the change in MD-CRS part II total score from baseline to week 15 (TEV-50717 versus placebo) will be compared using a 1-sided test for superiority at a nominal significance level of α=0.025.

The LS mean and standard error for the treatment groups, the LS mean difference, 2-sided 95% confidence interval, and p-value for the comparison (TEV-50717 versus placebo) at week 15 will be presented.

9.5.2.2. Sensitivity Analysis

To assess the robustness of the primary efficacy analysis, sensitivity analyses will include the following:

Sensitivity analyses for assumptions of missing data mechanism:

- tipping point (MNAR)
- MAR multiple imputation

Sensitivity analysis for the statistical model:

- analysis of covariance (ANCOVA)
- primary model, including only the following covariates: treatment group, week, and treatment group by week interaction

Other:

- primary model repeated for the ITT analysis set
- primary model repeated for the set of patients in the mITT analysis set that received at least 1 dose of IMP
- primary model repeated for the PP analysis set
- ANCOVA models for MD-CRS part II total score change from baseline to week 9 and to week 12

9.5.2.3. Minimal Clinically Important Difference and Minimal Clinically Important Change

To support the evaluation of the clinical impact of the change in dyskinesia as assessed by the primary endpoint, the minimal clinically important difference (MCID) and the minimal clinically important change (MCIC) will be calculated. The MCID and MCIC analyses will be performed based on 3 global impression of improvement anchors: caregiver (CaGI-I), investigator (CGI-I), and patient (PGI-I).

The MCID and MCIC analysis will be performed separately for each anchor (CaGI-I, CGI-I, and PGI-I) yielding a set of thresholds, each reflecting the perspective of the caregiver, the clinician, or the patient, depending on the anchor used.

The MCID and MCIC analyses will be based on the methods described by Hauser et al 2014 and Hauser et al 2022. Details will be provided in the statistical analysis plan.

9.5.3. Secondary Estimands

The secondary estimands are the differences in means between TEV-50717 and placebo in the target patient population for (1) change from baseline to week 15 in centrally read MD-CRS part I total score, (2) CaGI-I at week 15, (3) CGI-I at week 15, (4) change from baseline to week 15 in centrally read UHDRS-TMC, (5) change from baseline to week 15 in centrally read UHDRS-TMD, regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events.

The secondary estimands assess the effectiveness on patients' ability to perform daily functions, the improvement in dyskinesia evaluated by the caregiver and the investigator, and the reduction in chorea and dystonia evaluated by the central reviewers, all with a focus on the causal effects attributable to the IMP.

9.5.4. Key Secondary Endpoints

The key secondary endpoints are the following:

1. Change from baseline to week 15 in centrally read MD-CRS part I total score (TEV-50717 versus placebo)
2. CaGI-I at week 15 (TEV-50717 versus placebo)
3. CGI-I at week 15 (TEV-50717 versus placebo)
4. Change from baseline to week 15 in centrally read UHDRS-TMC (TEV-50717 versus placebo)
5. Change from baseline to week 15 in centrally read UHDRS-TMD (TEV-50717 versus placebo)

9.5.4.1. Secondary Efficacy Analysis

Analyses of the key secondary endpoints will be performed as follows:

1. MD-CRS part I total score change from baseline to week 15 will be analyzed using a mixed-effects model repeat measurement (MMRM) in the same fashion as the primary analysis, with the exception that the baseline value of MD-CRS part I total score will be included as the covariate instead of MD-CRS part II total score.
2. CaGI-I at week 15 will be analyzed using an MMRM model in the same fashion as the primary analysis, with the exceptions that the baseline value of CGI-S will be included as the covariate instead of MD-CRS part II total score and that week will include 5 levels (weeks 3, 7, 9, 12, and 15).
3. CGI-I at week 15 will be analyzed using an MMRM model in the same fashion as the primary analysis, with the exceptions that the baseline value of CGI-S will be included as the covariate instead of MD-CRS part II total score and that week will include 5 levels (weeks 3, 7, 9, 12, and 15).
4. UHDRS-TMC (centrally read) change from baseline to week 15 will be analyzed using an MMRM model in the same fashion as the primary analysis, with the exception that the baseline value of UHDRS-TMC (centrally read) will be included as the covariate instead of MD-CRS part II total score.
5. UHDRS-TMD (centrally read) change from baseline to week 15 will be analyzed using an MMRM model in the same fashion as the primary analysis, with the exception that the baseline value of UHDRS-TMD (centrally read) will be included as the covariate instead of MD-CRS part II total score.

In addition, sensitivity analyses for the key secondary endpoints will be performed in the same fashion as the primary endpoint.

9.5.5. Other Efficacy Endpoints

Other efficacy endpoints (change from baseline to week 15/proportion at week 15; TEV-50717 versus placebo) are the following:

- MD-CRS part I total score (general assessment, physician rated)

- MD-CRS part II total score (general assessment, physician rated)
- MD-CRS Global Index (calculated from MD-CRS parts I and II total scores)
- UHDRS-TMS (physician rated)
- UHDRS-TMC (physician rated)
- UHDRS-TMD (physician rated)
- PEDI-CAT (ADL, caregiver completed, content-balanced version)
- The CP module of the PedsQL (QoL, patient/caregiver)
- PGI-I Scale (global, patient/caregiver)
- CGI-S Scale (global, physician rated)
- CaGI-I response, defined as patients who are described by the caregiver as "Much Improved" or "Very Much Improved" in the CaGI-I score
- CGI-I response, defined as patients who are described as "Much Improved" or "Very Much Improved" in the CGI-I score
- CGI-S response, defined as patients who have a reduction of ≥1 point in the CGI-S score
- PGI-I response, defined as patients who are described as "Much Improved" or "Somewhat Improved" in the PGI-I score

9.5.5.1. Other Efficacy Analysis

Analysis methods will be provided in the SAP.

9.6. Multiple Comparisons and Multiplicity

The primary efficacy endpoint will be tested at the 1-sided significance level of α=0.025.

If the primary endpoint is statistically significant (p-value ≤0.025), the 5 key secondary hypotheses will be tested using a hierarchical approach at the 1-sided significance level of α=0.025, in the following order: (1) MD-CRS part I total score, (2) CaGI-I, (3) CGI-I, (4) UHDRS-TMC (centrally read), and (5) UHDRS-TMD (centrally read).

[redacted]

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

9.7. Planned Interim Analysis

This is the first study to evaluate the efficacy of TEV-50717 to reduce the severity of dyskinetic involuntary movements associated with CP in pediatric patients with DCP. Moreover, limited data are available on the effect of active treatment on MD-CRS part II total score in DCP that can support sample size calculations. Therefore, an IA for futility is planned.

When approximately 50 patients have completed the study (including follow-up), an iDMC will perform an unblinded non-binding IA for futility based on centrally read MD-CRS part II total score.

The rules for futility recommendation (eg, definition of the promising zone) will be included in the iDMC charter and the SAP. The iDMC charter will also provide the wording that will be used to communicate the iDMC recommendation. The SAP will be finalized before the IA will be performed.

9.8. Safety Endpoints and Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.3).

Safety assessments and time points are provided in Table 3.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. 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 (overall and by severity), adverse events determined by the investigator to be related to test IMP (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. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory, ECG, and vital signs measurements data will be summarized descriptively. ECG and vital signs values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics.

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 baseline, 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.

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

9.9. Tolerability Analysis

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

9.10. Pharmacokinetic/Pharmacodynamic Analysis

9.11. 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 SAP, 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 International Council for Harmonisation Harmonised Tripartite Guideline, Guideline for GCP E6, and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [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 IRB, 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 diseases 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 21CFR Part 54), the investigator will provide the sponsor with financial information required to complete the 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 05 Dated 24 March 2022

The reasons for this amendment are 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 3 (Study Procedures and Assessments) 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		
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. ~~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).~~	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.	New information indicates Naxibimols and Dalfampridine will not be used for DCP and therefore not relevant to this protocol.
1.1.1. Background for TEV-50717		
~~TEV-50717~~ IMP tablets are available in the following dose strengths:…	IMP tablets are available in the following dose strengths:…	Clarification

Protocol text with changes shown	New wording	Reason/justification for change
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 ~~with clinical conduct and analysis concluded and clinical study report (CSR) finalization pending~~ • One terminated Phase 3 long-term safety study in patients with TS ~~with analysis of results ongoing~~	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.
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	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 long-term TS study

Protocol text with changes shown	New wording	Reason/justification for change
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
2.1. Primary and Secondary Study Objectives and Endpoints		
See new wording column	• UHDRS-TMC (centrally read) • UHDRS-TMD (centrally read)	New key secondary endpoint
2.1.2. Primary and Secondary Estimands		
The secondary estimands are the differences in means between TEV-50717 and placebo in the target patient population for (1) change from baseline to week 15 in centrally read MD-CRS part I total score; (2) Caregiver Global Impression of Improvement (CaGI-I) at week 15; (3) Clinical Global Impression of Improvement (CGI-I) at week 15; (4) change from baseline to week 15 in centrally-read UHDRS-TMC; and (5) change from baseline to week 15 in centrally-read UHDRS-TMD, regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events. The primary estimand assesses the effectiveness in the reduction of choreiform movements in patients with DCP with predominant choreiform movement disorder, as evaluated by the central reviewers, focusing on the causal effects attributable to the IMP. The secondary estimands assess the effectiveness on patients' ability to perform daily functions, the improvement in dyskinesia evaluated by the caregiver and the investigator, and the reduction in chorea and dystonia evaluated by central reviewers, all with a focus on the causal effects attributable to the IMP.	The secondary estimands are the differences in means between TEV-50717 and placebo in the target patient population for (1) change from baseline to week 15 in centrally read MD-CRS part I total score, (2) Caregiver Global Impression of Improvement (CaGI-I) at week 15, (3) Clinical Global Impression of Improvement (CGI-I) at week 15, (4) change from baseline to week 15 in centrally-read UHDRS-TMC, and (5) change from baseline to week 15 in centrally-read UHDRS-TMD, regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events. The primary estimand assesses the effectiveness in the reduction of choreiform movements in patients with DCP with predominant choreiform movement disorder, as evaluated by the central reviewers, focusing on the causal effects attributable to the IMP. The secondary estimands assess the effectiveness on patients' ability to perform daily functions, the improvement in dyskinesia evaluated by the caregiver and the investigator, and the reduction in chorea and dystonia evaluated by central reviewers, all with a focus on the causal effects attributable to the IMP.	Text revised to account for new key secondary endpoints

Protocol text with changes shown	New wording	Reason/justification for change
3.1. General Study Design and Study Schematic Diagram		
… the first dose increase ~~may~~should be performed in an interval less than 5 days, only once, on day 3.	… the first dose increase should be performed in an interval less than 5 days, only once, on day 3.	Revised to match other instances in protocol
The following was deleted: ~~When approximately 90 patients have completed the study (including follow-up), an iDMC will perform an unblinded IA for futility and sample size re-estimation based on centrally read MD-CRS part II total score. Based on the results of the IA, the study may be stopped or the sample size may be kept as planned (approximately 185 total patients) or increased (up to approximately 230 total patients) (Section 9.7).~~		Text deleted to account for the change in sample size and the removal of the second IA for sample size reassessment
There is a separate protocol ~~will be issued~~ for the open-label safety extension Study TV50717-CNS-30081~~, as applicable~~.	There is a separate protocol for the open-label safety extension Study TV50717-CNS-30081.	The open-label extension has been approved for use.
Figure 1:Overall Study Schematic Diagram		
See new wording column	Figure 1 has been revised as described below: • Footnote was edited to clarify dose increases should be performed *after remote or in-clinic visits.*	Clarification
3.2. Planned Number of Patients and Regions		
Approximately ~~185~~65 patients are planned to be randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately ~~124~~43 in the TEV-50717 group; approximately ~~61~~22 in the placebo group) stratified by age at baseline (6 to <12 years; 12 through 18 years) and region (US; non-US). ~~The sample size will be re-estimated in an interim analysis and may be adjusted up to a total of approximately 230 patients.~~	Approximately 65 patients are planned to be randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 43 in the TEV-50717 group; approximately 22 in the placebo group) stratified by age at baseline (6 to <12 years; 12 through 18 years) and region (US; non-US).	Text revised to account for the change in sample size and the removal of the second interim analysis
This study is planned to be conducted in approximately ~~70~~ 60 investigational centers in North America, Asia, and Europe. ~~The study is expected to start by end of 2018 and last until the fourth quarter of 2022.~~	This study is planned to be conducted in approximately 60 investigational centers in North America, Asia, and Europe.	The expected end of the study changed to account for current pace of enrollment

Protocol text with changes shown	New wording	Reason/justification for change
3.4. Stopping Rules for the Study		
The following was deleted: ~~When approximately 90 patients have completed the study (including follow-up), an iDMC will perform an unblinded IA for futility and sample size re-estimation based on the primary endpoint, the centrally read MD-CRS part II total score. Based on the results of the IA, the study may be stopped for futility. For further details, see Section 9.~~		Text revised to account for the change in sample size and the removal of the second interim analysis
Table 3: Study Procedures and Assessments		
See new wording column	Table 3 has been revised as described below: • The time for the follow-up visits 16 and 17 was clarified. • The new endpoints (UHDRS-TMC and UHDRS-TMD) were added. • For the efficacy endpoints, assessments were added for possible unscheduled visits. • For the telephone contact visits, "Contact RTSM" was removed. • The footnotes were revised to make consistent with the changes to the table and the body of the protocol.	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		
11. 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.	11. 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	13. In patients who experience signs of suicidal ideation or behavior (Section 7.9), the investigator should consult with the medical monitor to determine whether the patient should continue in the study.	Added to align with Section 7.9

Protocol text with changes shown	New wording	Reason/justification for change
Table 4: Maximum Daily Dose of IMP During the Titration Period by Day and Weight Category at Baseline		
See new wording column	Table 4 has been revised as described below: • The first column for study visit was changed from days to weeks. • The footnotes were revised to make consistent with the changes to the table and the body of the protocol.	Revised for clarity
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 4 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 telephone or in-clinic visit.	• During the titration period, the dose of IMP should be adjusted according to Table 4 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 telephone or in-clinic visit.	Revised for clarity

Protocol text with changes shown	New wording	Reason/justification for change
Table 4: Maximum Daily Dose of IMP During the Titration Period by Week and Weight Category at Baseline		
See new wording column	Table 4 has been revised as described below: • The title was changed from "by 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.	Clarification
5.4. Treatment after the End of the Study		
All patients will discontinue IMP at the week 15 visit and will return 1 week later for the EOS visit. [redacted] Patients will not receive the evening IMP dose on this day. [redacted]	All patients will discontinue IMP at the week 15 visit and will return 1 week later for the EOS visit. [redacted] atients will not receive the evening IMP dose on this day.	Revised for clarity
Note: Patients can also roll over to the extension study within 2 to 4 weeks after the week 15 visit but will be required to complete additional scales and tests as part of Study TV50717-CNS-30081. ~~Patients will further be allowed to roll over to Study TV50717-CNS-30081 between 4 weeks and up to 6 months from the week 15 visit and will be subject to the full screening process. More details are presented in the TV50717-CNS-30081 protocol.~~	Note: Patients can also roll over to the extension study within 2 to 4 weeks after the week 15 visit but will be required to complete additional scales and tests as part of Study TV50717-CNS-30081.	Text deleted to loosening restrictions regarding COVID-19
5.7. Procedures for Monitoring Patient Compliance		
See new wording column	Based on pill counts at in-clinic visits, poor compliance with study drug intake (ie, <80%) or overdose (ie, >105%) is to be recorded as an important deviation and expeditiously reported to the medical monitor.	Added to define compliance

Protocol text with changes shown	New wording	Reason/justification for change
5.9. Randomization and Blinding		
In addition, the sponsor's clinical personnel and all vendors (with the exception of the sponsor's clinical supply chain staff and RTSM vendor) will be blinded to the IMP identity until the database has been locked for analysis and the treatment assignments are revealed.	In addition, the sponsor's clinical personnel and all vendors (with the exception of the sponsor's clinical supply chain staff and RTSM vendor) will be blinded to the IMP identity until the database has been locked for analysis and the treatment assignments are revealed.	Clarification
The iDMC will perform ~~one~~an unblinded non-binding IA for futility~~, another unblinded IA for futility and sample size reassessment~~ and will monitor safety throughout the study based on unblinded data.	The iDMC will perform an unblinded non-binding IA for futility and will monitor safety throughout the study based on unblinded data.	Text revised to account for the change in sample size and the removal of the second interim analysis
5.10.3. Independent Data Monitoring Committee		
The following was deleted: ~~When approximately 90 patients have completed the study (including follow-up), the iDMC will perform an unblinded IA for futility and sample size re-estimation based on centrally read MD-CRS part II total score. Based on current initial assumptions, the study may be stopped or the sample size may be kept as planned (approximately 185 total patients) or increased (up to approximately 230 total patients). The iDMC will also perform regular safety monitoring throughout the study.~~		Text deleted to account for the change in sample size and the removal of the second interim analysis
6.2.Key Secondary Efficacy Measures		
See new wording column	6.2.4. Unified Huntington's Disease Rating Scale-Total Maximal Chorea	New section added to account for the addition of a new key secondary endpoint
See new wording column	6.2.5. Unified Huntington's Disease Rating Scale-Total Maximal Dystonia	New section added to account for the addition of a new key secondary endpoint

Protocol text with changes shown	New wording	Reason/justification for change
6.2.4.Unified Huntington's Disease Rating Scale-Total Maximal Chorea		
The following text was moved from a later section to this new section: 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).		Text moved as this is the first mention of UHDRS-TMC rather than later
See new wording column	A central reading of the UHDRS-TMC will be performed at baseline and at weeks 9, 12, 15/ET, and 16/EOS 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 endpoint
6.2.5. Unified Huntington's Disease Rating Scale-Total Maximal Dystonia		
The following text was moved from a later section to this new section: The UHDRS-Total Maximal Dystonia (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). When rating dystonia (question #11), buccal-oral-lingual and facial dystonia (blepharospasm, jaw opening and closing) should be included in the assessment of the truncal region.		Text moved as this is not the first mention of UHDRS-TMD rather than in the later section

Protocol text with changes shown	New wording	Reason/justification for change
See new wording column	A central reading of the UHDRS-TMD will be performed at baseline and at weeks 9, 12, 15/ET, and 16/EOS 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 a new endpoint
6.3. Other Efficacy Measures		
See new wording column	6.3.1. Movement Disorder-Childhood Rating Scale Part I and Part II Total Scores	New section added for clarification – the numbering for the rest of the subsections were increased by one but this change was not noted here.
6.3.1. Movement Disorder-Childhood Rating Scale Part I and Part II Total Scores		
See new wording column	The MD-CRS part I and part II total scores will be evaluated by the investigator at baseline, week 9, week 12, week 15/ET, and week 16/EOS visits. See Section 6.1 and Section 6.2.1 for description of these rating scales.	New text added for clarification
6.3.3. Unified Huntington's Disease Rating Scale-Total Motor Score		
See new wording column	The protocol refers to UHDRS-TMS 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-TMS.	Text added to clarify the role of physicians for this efficacy measure
6.3.4. Unified Huntington's Disease Rating Scale-Total Maximal Chorea		
See new wording column	The UHDRS-TMC is administered at baseline, week 9, week 12, and week 15/ET visits, and will be rated by the investigator.	New text added for clarification

Protocol text with changes shown	New wording	Reason/justification for change
6.3.5. Unified Huntington's Disease Rating Scale-Total Maximal Dystonia		
See new wording column	The UHDRS-TMD is administered at baseline, week 9, week 12, and week 15/ET visits, and will be rated by the investigator.	New text added for clarification
7.2.1. Children's Columbia-Suicide Severity Rating Scale		
See new wording column	The children's C-SSRS questionnaire will be presented to patients ≥12 years of age at screening or 11 years of age at screening but will turn 12 years of age during the study.	Clarification
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
7.8. 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 a central diagnostic center will be interpreting the ECG.	Clarification

Protocol text with changes shown	New wording	Reason/justification for change
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
Note: Abnormal ECG results at week 3 and week 7 or at an unscheduled visit may result in patient withdrawal from the study as detailed in Section 4.3.	Note: Abnormal ECG results at week 3 and week 7 or at an unscheduled visit may result in patient withdrawal from the study as detailed in Section 4.3.	Clarification
9.1. Sample Size and Power Considerations		
See new wording column	At the time of writing Amendment 05, the initially planned sample size has been reduced to approximately 65 patients randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 43 in the TEV-50717 group; approximately 22 in the placebo group).	Text added to explain for the change in sample size due to study feasibility

Protocol text with changes shown	New wording	Reason/justification for change
The following was deleted: ~~The sample size may be adjusted in the IA to a maximal number of approximately 230 patients. The maximal sample size was chosen based on practical considerations, given the limited population of patients with DCP.~~ ~~Simulations for the study, including the IA for futility and sample size re-estimation, and the corresponding statistical methods to control the Type I error rate were performed. The overall power was approximately 83% under the initial assumptions and the overall Type I error rate of less than 0.025 for the primary analysis was confirmed. Further simulations were performed to evaluate the power and additional operating characteristics of the study under different assumptions of the effect size.~~		Text deleted to account for the change in sample size and the removal of the second interim analysis
9.3.1. Handling Withdrawals and Missing Data		
For all other cases, and for cases classified as above, classification as MAR/MNAR will be done/revisited in a blinded manner on a case-by-case basis prior to the IA for futility~~, the IA for futility and sample size reassessment~~ and prior to database lock for final analysis.	For all other cases, and for cases classified as above, classification as MAR/MNAR will be done/revisited in a blinded manner on a case-by-case basis prior to the IA for futility and prior to database lock for final analysis.	Text revised to account for the removal of the second interim analysis
9.4.1. Patient Disposition		
Data from patients screened; patients screened but not randomized (and reason not randomized); patients who are randomized; patients randomized but not treated; patients re-randomized; patients in the ITT, mITT, safety, and PP analysis sets; patients who complete the treatment period; patients who complete the EOS visit; ~~patients who intend to enroll into the open-label extension study; patients who do not intend to be enrolled into the open-label extension 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.	Data from patients screened; patients screened but not randomized (and reason not randomized); patients who are randomized; patients randomized but not treated; patients re-randomized; patients in the ITT, mITT, safety, and PP analysis sets; patients who complete the treatment period; patients who complete the EOS visit; 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.	Text deleted; these analyses will not be done

Protocol text with changes shown	New wording	Reason/justification for change
9.5.1. Primary Estimand		
The primary estimand assesses the effectiveness in the reduction of choreiform movements in patients with DCP with predominant choreiform movement disorder, evaluated by the central reviewers, focusing on the causal effects attributable to the IMP.	The primary estimand assesses the effectiveness in the reduction of choreiform movements in patients with DCP with predominant choreiform movement disorder, evaluated by the central reviewers, focusing on the causal effects attributable to the IMP.	Text added to account for new key secondary endpoints
9.5.2. Primary Endpoint		
See new wording column	9.5.2.3. Minimal Clinically Important Difference and Minimal Clinically Important Change	New section added to account for new analyses
9.5.2.3. Minimal Clinically Important Difference and Minimal Clinically Important Change		
See new wording column	To support the evaluation of the clinical impact of the change in dyskinesia as assessed by the primary endpoint, the minimal clinically important difference (MCID) and the minimal clinically important change (MCIC) will be calculated. The MCID and MCIC analyses will be performed based on 3 global impression of improvement anchors: caregiver (CaGI-I), investigator (CGI-I), and patient (PGI-I). The MCID and MCIC analysis will be performed separately for each anchor (CaGI-I, CGI-I, and PGI-I) yielding a set of thresholds, each reflecting the perspective of the caregiver, the clinician, or the patient, depending on the anchor used. The MCID and MCIC analyses will be based on the methods described by Hauser et al 2014 and Hauser et al 2022. Details will be provided in the statistical analysis plan.	New analyses

Protocol text with changes shown	New wording	Reason/justification for change
9.5.3 Secondary Estimands		
The secondary estimands are the differences in means between TEV-50717 and placebo in the target patient population for (1) change from baseline to week 15 in centrally read MD-CRS part I total score; (2) CaGI-I at week 15; (3) CGI-I at week 15; <u>(4) change from baseline to week 15 in centrally read UHDRS-TMC; (5) change from baseline to week 15 in centrally read UHDRS-TMD,</u> regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events. The secondary estimands assess the effectiveness on patients' ability to perform daily functions, the improvement in dyskinesia evaluated by the caregiver and the investigator, <u>and the reduction in chorea and dystonia evaluated by the central reviewers, all</u> with a focus on the causal effects attributable to the IMP.	The secondary estimands are the differences in means between TEV-50717 and placebo in the target patient population for (1) change from baseline to week 15 in centrally read MD-CRS part I total score, (2) CaGI-I at week 15, (3) CGI-I at week 15, (4) change from baseline to week 15 in centrally read UHDRS-TMC, (5) change from baseline to week 15 in centrally read UHDRS-TMD, regardless of whether or not dose reduction, suspension, or discontinuation occurred, and regardless of treatment-related adverse events. The secondary estimands assess the effectiveness on patients' ability to perform daily functions, the improvement in dyskinesia evaluated by the caregiver and the investigator, and the reduction in chorea and dystonia evaluated by the central reviewers, all with a focus on the causal effects attributable to the IMP.	Text updated to account for new key secondary endpoints
9.5.4. Key Secondary Endpoints		
See new wording column	4. Change from baseline to week 15 in centrally read UHDRS-TMC (TEV-50717 versus placebo) 5. Change from baseline to week 15 in centrally read UHDRS-TMD (TEV-50717 versus placebo)	New key secondary endpoints

Protocol text with changes shown	New wording	Reason/justification for change
9.5.4.1. Secondary Efficacy Analysis		
See new wording column	4. UHDRS-TMC (centrally read) change from baseline to week 15 will be analyzed using an MMRM model in the same fashion as the primary analysis, with the exception that the baseline value of UHDRS-TMC (centrally read) will be included as the covariate instead of MD-CRS part II total score. 5. UHDRS-TMD (centrally read) change from baseline to week 15 will be analyzed using an MMRM model in the same fashion as the primary analysis, with the exception that the baseline value of UHDRS-TMD (centrally read) will be included as the covariate instead of MD-CRS part II total score.	New key secondary analyses for the new endpoints
9.6. Multiple Comparisons and Multiplicity		
If the primary endpoint is statistically significant (p-value ≤0.025), the 5 key secondary hypotheses will be tested using a hierarchical approach at the 1-sided significance level of α=0.025, in the following order: (1) MD-CRS part I total score, (2) CaGI-I, ~~and~~ (3) CGI-I, (4) UHDRS-TMC (centrally read), and (5) UHDRS-TMD (centrally read).	If the primary endpoint is statistically significant (p-value ≤0.025), the 5 key secondary hypotheses will be tested using a hierarchical approach at the 1-sided significance level of α=0.025, in the following order: (1) MD-CRS part I total score, (2) CaGI-I, (3) CGI-I, (4) UHDRS-TMC (centrally read), and (5) UHDRS-TMD (centrally read).	New key secondary analyses for the new endpoints
9.7. Planned Interim Analysis		
This is the first study to evaluate the efficacy of TEV-50717 to reduce the severity of dyskinetic involuntary movements associated with CP in pediatric patients with DCP. Moreover, limited data are available on the effect of active treatment on MD-CRS part II total score in DCP that can support sample size calculations. Therefore, an IA~~s~~ for futility ~~and sample size re-estimation are~~ is planned. ~~Based on current initial assumptions, 185 patients is the sample size required to obtain a statistically significant result in the primary analysis with a power of approximately 90% (see Section 9.1).~~	This is the first study to evaluate the efficacy of TEV-50717 to reduce the severity of dyskinetic involuntary movements associated with CP in pediatric patients with DCP. Moreover, limited data are available on the effect of active treatment on MD-CRS part II total score in DCP that can support sample size calculations. Therefore, an IA for futility is planned.	Text revised to account for the change in sample size and the removal of the second interim analysis

Protocol text with changes shown	New wording	Reason/justification for change
The following text was deleted: ~~When approximately 90 patients have completed the study (including follow-up), an iDMC will perform an unblinded IA for futility and sample size re-estimation based on centrally read MD CRS part II total score.~~ ~~The sample size re-estimation will be performed using the promising zone approach (Mehta and Pocock 2011). At the IA, the conditional power for the initially planned sample size of approximately 185 patients will be estimated given the observed data, and the sample size may be increased up to a total maximum of approximately 230 patients.~~ ~~The Type I error rate will be controlled using the Chen, DeMets, and Lan method (Chen et al 2004); hence, α=0.025 will be used for the primary analysis.~~		Text deleted to account for the change in sample size and the removal of the second interim analysis
The rules for futility recommendation ~~in the first IA, and the futility and sample size re-estimation in the second IA~~ (eg, definition of the promising zone) will be included in the iDMC charter and the SAP.	The rules for futility recommendation (eg, definition of the promising zone) will be included in the iDMC charter and the SAP.	Text revised to account for the change in sample size and the removal of the second interim analysis
9.8. 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 and by treatment group.	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.	Clarification
9.10. Pharmacokinetic/Pharmacodynamic Analysis		
[redacted]	[redacted]	[redacted]

Protocol text with changes shown	New wording	Reason/justification for change
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.~~ ~~Chen YH, DeMets DL, Lan KK. Increasing the sample size when the unblinded interim result is promising. Stat Med 2004;23(7):1023-38.~~ ~~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~~ ~~Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med 2011;30(28):3267-84.~~		References deleted to account for the change in sample size and the removal of the second interim analysis as well changes in the introduction
See new wording column	Hauser RA, Barkay H, Wilhelm A, Wieman M, Savola J-M, Gordon MF. Minimal clinically important change in abnormal involuntary movement scale score in tardive dyskinesia as assessed in pivotal trials of deutetrabenazine. Parkinsonism Related Disorders. *In Press*. Hauser RA, Gordon MF, Mizuno Y, Poewe W, Barone P, Schapira AH, et al. Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. Parkinsons Dis. 2014;2014:467131.	New key secondary analyses for the new endpoints
AUSTEDO® (deutetrabenazine) tablets (US prescribing information). Teva Pharmaceuticals USA, Inc; ~~2019~~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

Protocol text with changes shown	New wording	Reason/justification for change
APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Row: Sponsor's Authorized Representative Column: [redacted] Teva Branded Pharmaceutical ~~Industries,~~ [redacted] roducts R&D, Inc Cell: [redacted]	Row: Sponsor's Authorized Representative Column: [redacted] Teva Branded Pharmaceutical Products R&D, Inc Cell: [redacted]	Administrative change
Row: Sponsor's Representative of Global Patient Safety and Pharmacovigilance Column: [redacted] Teva Pharmaceutical Industries, [redacted] Tel: [redacted] Cell: [redacted]	Row: Sponsor's Representative of Global Patient Safety and Pharmacovigilance Column: [redacted] Teva Pharmaceutical Industries, [redacted] Tel: [redacted] Cell: [redacted]	Administrative change
Row: Randomization and 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: Randomization and Trial Supply Management (RTSM) 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
APPENDIX B. INDEPENDENT DATA MONITORING COMMITTEE		
The following was deleted: ~~When approximately 90 patients have completed the study (including follow-up), an iDMC will perform an unblinded IA for futility and sample size re-estimation based on centrally read MD-CRS part II. Based on the results of the IA, the study may be stopped or the sample size may be kept as planned (approximately 185 total patients) or increased (up to approximately 230 total patients).~~		Text deleted to account for the change in sample size and the removal of the second interim analysis
APPENDIX C. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
3. Procedures During Administration of Investigational Medicinal Product (Double-Blind Treatment Period Inclusive of Titration Period)		
a. Week 1 (day 7+1 day), week 2 (day 14±3 days total from baseline), week 4 (day 28±3 days total from baseline), week 5 (day 35±3 days total from baseline), and week 6 (day 42±3 days total from baseline)		
The following was deleted: • ~~contact RTSM~~		Study procedures and assessments have been updated for consistency with changes made to the protocol body and Table 3. This justification applies to all changes indicated within Appendix C.
4. Procedures During Administration of Investigational Medicinal Product (Maintenance Period)		
a. Week 9 (day 63±3 days total from baseline) and week 12 (day 84±3 days total from baseline)		
See new wording column	• urine pregnancy test (week 12 only)	
5. Follow-Up (Weeks 16 and 17)		
a. Week 16/End of Study follow-up visit (~~day 112~~ 1 week±2 days total from the week 15 visit~~baseline~~)	a. Week 16/End of Study follow-up visit (1 week±2 days total from the week 15/ET visit)	
b. Week 17 follow-up visit (~~day 119~~2 weeks±2 days total from week 15 visit~~baseline~~, or 2 weeks after ET visit)	b. Week 17 follow-up visit (2 weeks±2 days total from week 15 visit, or 2 weeks after ET visit)	

Protocol text with changes shown	New wording	Reason/justification for change
6. Unscheduled Visits		
Procedures performed during unscheduled visits may include any of the following:	Procedures performed during unscheduled visits may include any of the following:	
See new wording column	• MD-CRS part I video recording and investigator assessment • MD-CRS part II video recording and investigator assessment • CaGI-I (global, caregiver rated) • CGI-I and CGI-S (global, physician rated) • PEDI-CAT (ADL, caregiver completed, content-balanced version) • PedsQL (QoL, patient/caregiver) • PGI-I (global, patient/caregiver) • UHDRS-TMS	
APPENDIX H. LIST OF ALLOWED AND PROHIBITED MEDICATIONS		
Table 10: Allowed Medications Row: Benzodiazepines, trihexyphenidyl, … Column: Condition The following text was deleted: ~~Primary use must not be for dyskinesia chorea…~~		Clarification
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 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 affecting normal per-protocol conduct of the study.	Text revised due to the ongoing, changing nature of the COVID-19 pandemic

16.2. Administrative Letter 07 Dated 05 May 2021

ADMINISTRATIVE LETTER 07

Study number: TV50717-CNS-30080

Clinical Study Protocol with Amendment 04

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents

Version date 09 March 2021

IND number: 139700; EudraCT number: 2018-003742-17

05 May 2021

Dear Investigator:

The purpose of this letter is to clarify details in the Study Protocol on study drug storage temperature, timing of dosing, and study duration.

1. In **Section 5.2.1 Storage and Security** of the Study Protocol, it is stated that "The IMPs (TEV-50717 and placebo IMP) must be stored at a controlled room temperature, 20°C to 25°C (68°F to 77°F), in a securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff." In Table 6 (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 11** of the Pharmacy Manual, 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°-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 referral to the Pharmacy Manual as follows:

   Section 5.2.1 Storage and Security:

   "The IMPs (TEV-50717 and placebo IMP) must be stored at a controlled room temperature, 20°C to 25°C (68°F to 77°F), in a securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff. **For additional information related to the IMP storage condition please refer to Section 11 of the Pharmacy Manual**."

   Table 6:

   A footnote will be added to Table 6 with attention to storage conditions as follows: "**For additional information related to the IMP storage condition please refer to Section 11 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 4 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". To clarify and ensure that study drug dose adjustments are made on the day following a phone call visit or site visit, the following footnote will be added to Table 4 (similar to footnote 'j' in Table 3): "**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 IMP at the Week 15 visit and will return 1 week later for the EOS visit". The sponsor would like to clarify that at the Week 15 visit, the patient does not receive a full daily dose, but is expected to take only the morning dose for the PK sample. Therefore, footnote 'p' in Table 3 and Section 5.4 will be adjusted as follows:

   Footnote 'p' Table 3: "Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected 2 to 3 hours after the first pharmacokinetic sample collection. Patients with early morning visits (ie, within 2 hours of their scheduled morning dosing) should take their IMP dose in clinic after the first pharmacokinetic sample is collected. **The patient will not continue dosing after PK sample collection and will not complete the full daily dose on the day of the Week-15 visit**".

   Section 5.4: "All patients will discontinue IMP at the week 15 visit and will return 1 week later for the EOS visit. **Patients will not continue dosing after PK sample collection and will not complete the full daily dose on the day of the Week-15 visit**. Patients who complete the study may be eligible to begin participation in the open label safety extension Study TV50717-CNS-30081".
4. The **Synopsis** of the Study Protocol (Page 7) states "Planned Study Period: Fourth quarter of 2018 to fourth quarter of 2021". To align with the ICF, which indicates the study will end in the **fourth quarter of 2022**, the "Planned Study Period" will be adjusted as follows: "Planned Study Period: Fourth quarter of 2018 to fourth quarter of 202~~1~~**2**".

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]

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[redacted]

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16.3. Amendment 04 Dated 09 March 2021

The reasons for this amendment are to clarify some of the inclusion/exclusion criteria, the addition of an IA for futility, to clarify the collection of additional blood samples due to discontinuation due to adverse events, and to clarify the manner in which patients will be enrolled into the open-label extension Study TV50717-CNS-30081.

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

Protocol text with changes shown	New wording	Reason/justification for change
1.1. Introduction		
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).	Added one of the causes of CP and added the NINDS reference to support this addition.
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.	Clarified the form of DCP
1.2.2. Clinical Studies		
The clinical development plan for TEV-50717 to date includes the following: • ~~Nine~~Thirteen completed Phase 1 studies in healthy adult volunteers • Two ~~ongoing~~completed pivotal studies in patients with TS with clinical conduct and analysis concluded and clinical study report (CSR) finalization pending • One terminated Phase 3 long-term safety study in patients with TS with analysis of results ongoing	The clinical development plan for TEV-50717 to date includes the following: • Thirteen completed Phase 1 studies in healthy adult volunteers • Two completed pivotal studies in patients with TS with clinical conduct and analysis concluded and clinical study report (CSR) finalization pending • One terminated Phase 3 long-term safety study in patients with TS with analysis of results ongoing	Updated the status of the TEV-50717 studies that have been conducted/completed since the last amendment.
1.2.2.1. Clinical Pharmacology Studies		
~~Nine~~Thirteen Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers.	Thirteen 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.
1.2.2.2. Clinical Safety and Efficacy Studies		
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,	Text added for safety results of recently completed TS studies

Protocol text with changes shown	New wording	Reason/justification for change
	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.	
2.1. Primary and Secondary Study Objectives and Endpoints (Other sections affected by anyone of these changes: 9.5.5)		
See new wording column	The following were added as other efficacy measures and endpoints: • MD-CRS part I total score (general assessment, physician rated) • MD-CRS part II total score (general assessment, physician rated)	Updated endpoints are in the Statistical Analysis Plan; added to the protocol for consistency.
• UHDRS-TMS (physician rated) • UHDRS-TMC (physician rated) • UHDRS-TMD (physician rated)	• UHDRS-TMS (physician rated) • UHDRS-TMC (physician rated) • UHDRS-TMD (physician rated)	Clarified these scales are to be rated by the physician
3.1. General Study Design and Study Schematic Diagram		
For patients who are minors, the caregiver is typically a parent or ~~legal guardian~~ a legally accepted representative. In some countries, an adult (such as grandparent or nurse) can be appointed by the parent or ~~legal guardian~~ legally accepted representative (as per local regulations and laws) and would take over this responsibility as a caregiver. The parent or ~~legal guardian~~ legally accepted representative only has to sign the parent/~~legal guardian~~ legally accepted representative informed consent form (ICF) and not the caregiver ICF. For adult patients, a caregiver must be appointed by the patient; this can be the parent, a ~~legal guardian~~ legally accepted representative, 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~~ legally accepted representative, ie, informed consent, withdrawal of consent, requests for discontinuation of the IMP, or withdrawal from the study for any reason. To	For patients who are minors, the caregiver is typically a parent or a legally accepted representative. In some countries, an adult (such as grandparent or nurse) can be appointed by the parent or legally accepted representative (as per local regulations and laws) and would take over this responsibility as a caregiver. The parent or legally accepted representative only has to sign the parent/legally accepted representative informed consent form (ICF) and not the caregiver ICF. For adult patients, a caregiver must be appointed by the patient; this can be the parent, a legally accepted representative, 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 accepted representative, ie, informed consent, withdrawal of consent, requests for discontinuation of the IMP, or withdrawal from the study for any reason. To further clarify, the caregiver is not allowed to make decisions on the child's	Clarified one of the terms for caregiver for patients who are minors

Protocol text with changes shown	New wording	Reason/justification for change
further clarify, the caregiver is not allowed to make decisions on the child's health or where "parent/~~ legal guardian~~ legally accepted representative" is specifically indicated in the protocol.	health or where "parent/legally accepted representative" is specifically indicated in the protocol.	
IMP will be titrated during the double-blind treatment period starting with 6 mg of TEV-50717 or matching placebo IMP in the morning of days 2 ~~and 3~~. Patients ~~with a~~ in the highest body weight group (≥40 kg/88 lbs) will ~~further dose in the~~ start an evening administration from ~~starting on~~ day 3 and for the remainder of the first week.	IMP will be titrated during the double-blind treatment period starting with 6 mg of TEV-50717 or matching placebo IMP in the morning of day 2. Patients in the highest body weight group (≥40 kg/88 lbs) will start an evening administration from day 3 and for the remainder of the first week.	Clarified when the dose may be increased for patients in the highest body weight group
~~After week 1,~~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 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 may be performed in an interval less than 5 days, only once, on day 3.	Clarified when the dose may be increased for patients in the highest body weight group
Washout period and follow-up: … At the week 16 visit, patients may choose to enter Study TV50717-CNS-30081 (on that day) or up to 1 week later (2 weeks from the week 15 visit). Patients who complete treatment~~,~~ but choose not to participate in the open-label safety extension Study TV50717-CNS-30081 any time before week 17 of Study TV50717-CNS-30080 will be contacted for a safety evaluation call occurring 2 weeks after their last dose of IMP. Additional details for patients to enter Study TV50717-CNS-30081 are provided in the TV50717-CNS-30081 protocol.	Washout period and follow-up: … At the week 16 visit, patients may choose to enter Study TV50717-CNS-30081 (on that day) or up to 1 week later (2 weeks from the week 15 visit). Patients who complete treatment but choose not to participate in the open-label safety extension Study TV50717-CNS-30081 any time before week 17 of Study TV50717-CNS-30080 will be contacted for a safety evaluation call occurring 2 weeks after their last dose of IMP. Additional details for patients to enter Study TV50717-CNS-30081 are provided in the TV50717-CNS-30081 protocol.	Clarified the timing of when a patient can enter Study TV50717-CNS-30081
See new wording column	When approximately 50 patients have completed the study (including follow-up), an independent Data Monitoring Committee (iDMC) will perform an unblinded non-binding interim analysis (IA) for futility based on centrally read MD-CRS part II total score.	Text added for the addition of the second interim analysis
When approximately 90 patients have completed the study (including follow-up), an iDMC will perform an unblinded IA for futility and sample size re-estimation based on centrally read MD-CRS part II total score.	When approximately 90 patients have completed the study (including follow-up), an iDMC will perform an unblinded IA for futility and sample size re-estimation based on centrally read MD-CRS part II total score.	Text updated to account for the second interim analysis

Protocol text with changes shown	New wording	Reason/justification for change
An iDMC charter will be developed for the IAs, and the procedures to ensure the integrity of the study will be provided in the charter.	An iDMC charter will be developed for the IAs, and the procedures to ensure the integrity of the study will be provided in the charter.	Text updated to account for the second interim analysis
At the time of informed consent, the parent/~~legal guardian~~ legally accepted representative will be…	At the time of informed consent, the parent/legally accepted representative will be…	Clarified one of the terms for caregiver for patients who are minors
See new wording column	Patients who screen fail or terminate early from the study due to emergency circumstances (such as coronavirus disease 2019 [COVID-19]) may be allowed to re-screen/re-enter (respectively) the study at a later date, depending on the circumstances. Each case should be referred to the medical monitor and approved in advance.	Text added to allow patients to re-enter study.
3.4. Stopping Rules for the Study and Section 5.10.3 Independent Data Monitoring Committee		
See new wording column	When approximately 50 patients have completed the study (including follow-up), an iDMC will perform an unblinded non-binding IA for futility based on the primary endpoint, the centrally read MD-CRS part II total score. Based on the results of the IA, the study may be stopped for futility.	Text added for the addition of the second interim analysis
Table 3: Study Procedures and Assessments		
See new wording column	Table 3 has been revised as described below: • The visit window for day 7 (week 1) was changed from ±1 day to +1 day and a new visit window for day 14 (week 2) was added • The visit window for the Titration and Maintenance Periods was revised to include ≥5 days from last dose change • [redacted] • For β-HCG test, the assessment at week 9 (day 63) was removed • An assessment for Contact RTSM was added • The footnotes were revised to make consistent with the	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
	changes to the table and the body of the protocol	
4.1. Patient Inclusion Criteria		
12. For a patient who is a minor, the parent(s)/~~legal guardian~~ legally accepted representative(s) provide written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide their own written informed consent (in accordance with local regulations) and the legally acceptable representative will sign, if needed. In this study, eligible patients are patients with dyskinetic CP who 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 assent/consent.	12. For a patient who is a minor, the parent(s)/legally accepted representative(s) provide written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide their own written informed consent (in accordance with local regulations) and the legally acceptable representative will sign, if needed. In this study, eligible patients are patients with dyskinetic CP who 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 assent/consent.	Text added to provide additional guidance in consideration of exclusion crtierion “i”
13. Caregivers provide written informed consent after being assigned the role by an adult patient, or if this role is delegated by the parent/~~legal guardian~~ legally accepted representative(s) of a patient who is a minor.	13. Caregivers provide written informed consent after being assigned the role by an adult patient, or if this role is delegated by the parent/legally accepted representative of a patient who is a minor.	Clarified one of the terms for caregiver for patients who are minors
4.2. Patient Exclusion Criteria		
2. Patient has clinically significant depression at screening or baseline. - Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening and anticipated to remain stable (dose and frequency) within the study duration.	2. Patient has clinically significant depression at screening or baseline. - Note: Patients receiving antidepressant therapy may be enrolled if on a stable dose for at least 6 weeks before screening and anticipated to remain stable (dose and frequency) within the study duration.	Clarified any antidepressant therapy received by the patient must remain stable throughout the study
3. Patient has a history of suicidal intent or related behaviors based on medical or psychiatric history or the C-SSRS within 2 years of screening:	3. Patient has a history of suicidal intent or related behaviors based on medical or psychiatric history or the C-SSRS within 2 years of screening:	Clarified how to assess the exclusion criterion

Protocol text with changes shown	New wording	Reason/justification for change
4. Patient has a history of a previous actual, interrupted, or aborted suicide attempt based on medical or psychiatric history or the C-SSRS.	4. Patient has a history of a previous actual, interrupted, or aborted suicide attempt based on medical or psychiatric history or the C-SSRS.	Clarified how to assess the exclusion criterion
Exclusion criteria #6 was deleted.		Upon further consideration of exclusion criterion #6, it was decided to remove the criteria surrounding BoNT and provide clarification in Appendix H.
~~7~~6. Patient has received any of the following concomitant medications ~~for dystonia or chorea~~ within the specified exclusionary windows of screening: ~~– Within 3 months: depot neurolepties~~ – Within 30 days: tetrabenazine, deutetrabenazine, or valbenazine – Within 21 days: reserpine – Within 14 days: ~~neurolepties (oral), typical and atypical antipsychotics (see Appendix H), metoclopramide,~~ levodopa, dopamine agonists, and MAOIs ~~– Note: Use of benzodiazepines, muscle relaxants, trihexyphenidyl, baclofen (oral and intrathecal), gabapentin, and levetiracetam is allowed if the dosing has been stable for at least 4 weeks before screening.~~ ~~– Note: Use of topiramate (up to 200 mg/day) is allowed if dosing has been stable for at least 4 weeks before screening.~~	6. Patient has received any of the following concomitant medications within the specified exclusionary windows of screening: – Within 30 days: tetrabenazine, deutetrabenazine, or valbenazine – Within 21 days: reserpine – Within 14 days: levodopa, dopamine agonists, and MAOIs	Clarified the concomitant medication types and criteria for patient exclusion
~~18~~17. Patient has a history of or acknowledges alcohol or other substance abuse in the 12 months before screening~~, as defined in the Diagnostic and Statistical Manual of Mental Disorders (version 5)~~.	17. Patient has a history of or acknowledges alcohol or other substance abuse in the 12 months before screening.	Clarified how to assess the exclusion criterion
~~19~~18. Patient has a positive urine drug screen test result (with exception of medications listed in ~~Table 9~~ Table 10 of Appendix H) ~~or is unable to refrain from~~	18. Patient has a positive urine drug screen test result (with exception of medications listed in Table 10 of Appendix H). Any request to include a patient with a	Clarified how patients with a positive urine result may be enrolled

Protocol text with changes shown	New wording	Reason/justification for change
~~substance abuse throughout the study~~. Any request to include a patient with a positive urine drug screen test result should be discussed with, and approved by, the medical monitor. Refer to Section 7.5.2.2 (urine drug screen) for more details.	positive urine drug screen test result should be discussed with, and approved by, the medical monitor. Refer to Section 7.5.2.2 (urine drug screen) for more details.	
4.3. Withdrawal Criteria and Procedures for the Patient		
See new wording column	5. Patient engages in alcohol or other substance abuse.	New reason for patients to be withdrawn
12. If a post-baseline QTcF value >500 msec or change from ~~baseline~~screening >60 msec is found, the investigator should repeat the ECG assessment twice more and compare the average of these 3 post-~~baseline~~ screening QTcF values to the~~and compare to the average of the 2~~ pre-treatment QTcF values ~~(baseline and~~ at screening~~) to the average of the 3 post-baseline QTcF values~~. The IMP must be stopped for any confirmed post-baseline QTcF average value >500 msec or average increase from ~~baseline~~screening >60 msec. In addition, a patient may be withdrawn from the study as described in Sections 3.4, 3.5, and 5.10 and Appendix C.	12. If a post-baseline QTcF value >500 msec or change from screening >60 msec is found, the investigator should repeat the ECG assessment twice more and compare the average of these 3 post-screening QTcF values to the pre-treatment QTcF values at screening. The IMP must be stopped for any confirmed post-baseline QTcF average value >500 msec or average increase from screening >60 msec. In addition, a patient may be withdrawn from the study as described in Sections 3.4, 3.5, and 5.10 and Appendix C.	Clarified when and how a change in QTcF would require study discontinuation
4.5. Rescreening		
See new wording column	For COVID-19 updates, refer to Appendix M.	Updated to cross-reference the addition to Appendix M
5.1.1.1. Starting Dose and Dose Levels		
Test IMP will be supplied in 20 count tablets per dose strength per bottle assembling 6, 12, 18, 24, 30, 36, 42, and 48 mg dose kit combinations.	Test IMP will be supplied in 20-count tablets per dose strength per bottle assembling 6, 12, 18, 24, 30, 36, 42, and 48 mg dose kit combinations.	Clarified the tablets in the dose kit

Protocol text with changes shown	New wording	Reason/justification for change
5.1.1.2. Dose Modification and Dose Stratification		
• IMP ~~cannot~~ should be swallowed whole. If the IMP is crushed or split ~~but should be swallowed whole~~, it should not be ingested; it should be replaced with a new tablet. The tablets will 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 swallowing difficulties.	• IMP should be swallowed whole. If the IMP is crushed or split, it should not be ingested; it should be replaced with a new tablet. The tablets will 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.	Clarified how study drug should be taken
• If there is only a single dose of IMP per day, the dose should be taken in the morning. However, ~~if a~~ patients experiencing 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.	• If there is only a single dose of IMP per day, the dose should be taken in the morning. However, patients experiencing somnolence while taking the 6-mg dose in the morning may switch to taking it as an evening dose for the rest of the days up to day 14.	Clarified wording
• The starting dose ~~is~~of 6 mg ~~in all for patients. This dose~~ will be administered in the morning on day~~s~~ 2 and for the remainder of the first week. Patients in the highest body weight group (≥40 kg/88 lbs) will start an evening administration from day 3 and~~, followed by evening administration starting on day 3~~ for the remainder of the first 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.~~ • ~~After week 1, dose increases may not occur more frequently than every 5 days.~~	• The starting dose of 6 mg will be administered in the morning on day 2 and for the remainder of the first week. Patients in the highest body weight group (≥40 kg/88 lbs) will start an evening administration from day 3 and for the remainder of the first week. 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.	Clarified when the dose may be increased for patients in the highest body weight group

Protocol text with changes shown	New wording	Reason/justification for change
See new wording column	• 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 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 last treatment kit back so the patient can take 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.	Clarified how study drug should be taken
• During the titration period, the dose of IMP should be adjusted ~~weekly~~ according to Table 4….	• During the titration period, the dose of IMP should be adjusted according to Table 4….	Clarified how study drug should be taken
Table 4: Maximum Daily Dose of IMP During the Titration Period by Day and Weight Category at Baseline		
See new wording column	The following footnote was added: a 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 be performed in an interval less than 5 days, only once, on day 3.	Footnote added to align against the updates in the body of the protocol
c. Patients <u>in this weight category</u> will receive the 6-mg once-daily dose in the morning on days ~~2 and 3~~, followed by ~~evening~~ twice-daily administration of 6 mg starting on day 3.	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.	Footnote updated to align against the updates in the body of the protocol
Table 6: Investigational Medicinal Products Used in the Study		
See new wording column	Row: Manufacturer Column: TEV-50717 Test IMP Anesta LLC 4745 Wiley Post Way Salt Lake City, UT 84116	Added new IMP manufacturer

Protocol text with changes shown	New wording	Reason/justification for change
See new wording column	Row: Manufacturer Column: Placebo IMP Anesta LLC 4745 Wiley Post Way Salt Lake City, UT 84116	Added new IMP manufacturer
Row: Storage conditions Column: TEV-50717 Test IMP Stored at controlled room temperature, 20°C-25°C (68°F-77°F)~~, protected from light and moisture~~	Row: Storage conditions Column: TEV-50717 Test IMP Stored at controlled room temperature, 20°C-25°C (68°F-77°F)	Clarified IMP storage stipulations
Row: Storage conditions Column: Placebo Test IMP Stored at controlled room temperature, 20°C-25°C (68°F-77°F)~~, protected from light and moisture~~	Row: Storage conditions Column: Placebo Test IMP Stored at controlled room temperature, 20°C-25°C (68°F-77°F)	Clarified IMP storage stipulations
5.2.1. Storage and Security		
The IMPs (TEV-50717 and placebo IMP) 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. ~~Diversion is considered to have occurred when the legal supply chain of prescription analgesic medicinal products is broken, and medicinal products are transferred from a licit to an illicit channel of distribution or use.~~	The IMPs (TEV-50717 and placebo IMP) must be stored at a controlled room temperature, 20ºC to 25ºC (68ºF to 77ºF), in a securely locked, substantially constructed cabinet or enclosure with access limited to authorized staff.	Clarified IMP storage stipulations
5.2.3. Accountability		
Each IMP shipment will include a packing slip listing the contents of the shipment~~, return instructions,~~ and any applicable forms.	Each IMP shipment will include a packing slip listing the contents of the shipment and any applicable forms.	Clarified the content of IMP packing slip
A record of IMP accountability (ie, IMP and other study materials received, used, 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,~~ Any used (partially used or empty) bottles and unused ~~bottles of IMP will be~~ kits/bottles that are	A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Any used (partially used or empty) bottles and unused kits/bottles that are not destroyed at the site are returned to	Clarified the instructions for IMP disposal

Protocol text with changes shown	New wording	Reason/justification for change
not destroyed at the site are returned to the sponsor or designee, as agreed with the sponsor (including expired and damaged kits).	the sponsor or designee, as agreed with the sponsor (including expired and damaged kits).	
5.4. Treatment after the End of the Study		
At the week 16 visit, patients may choose to enter Study TV50717-CNS-30081 (on that day) or up to 1 week later (2 weeks from the week 15 visit) ~~they will have an additional week to make a decision~~. Patients who complete treatment but choose not to participate in the open-label safety extension Study TV50717-CNS-30081 before week 17 of Study TV50717-CNS-30080 will be contacted for a safety evaluation call occurring 2 weeks after their last dose of IMP. Additional details for patients to enter Study TV50717-CNS-30081 are provided in the TV50717-CNS-30081 protocol.	At the week 16 visit, patients may choose to enter Study TV50717-CNS-30081 (on that day) or up to 1 week later (2 weeks from the week 15 visit). Patients who complete treatment but choose not to participate in the open-label safety extension Study TV50717-CNS-30081 before week 17 of Study TV50717-CNS-30080 will be contacted for a safety evaluation call occurring 2 weeks after their last dose of IMP. Additional details for patients to enter Study TV50717-CNS-30081 are provided in the TV50717-CNS-30081 protocol.	Clarified the timing of when a patient can enter Study TV50717-CNS-30081
See new wording column	Note: Patients can also roll over to the extension study within 2 to 4 weeks after the week 15 visit but will be required to complete additional scales and tests as part of Study TV50717-CNS-30081. Patients will further be allowed to roll over to Study TV50717-CNS-30081 between 4 weeks and up to 6 months from the week 15 visit and will be subject to the full screening process. More details are presented in the TV50717-CNS-30081 protocol.	Clarified the timing of when a patient can enter Study TV50717-CNS-30081
5.6. Prior and Concomitant Medication		
Caregivers and patients 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 if there is any change in current medications, including over-the-counter medications. Any prescribed new and/or any change in current medication should be reviewed with the investigator. Indication, dosage, and start and end dates should be entered on the CRF.	Caregivers and patients 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 if there is any change in current medications, including over-the-counter medications. Any prescribed new and/or any change in current medication should be reviewed with the investigator. Indication, dosage, and start and end dates should be entered on the CRF.	Clarified the investigator should be notified of any changes to current medications
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 ~~corrected for heart~~	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 prolongation	Clarified QT prolongation rather than QTc

Protocol text with changes shown	New wording	Reason/justification for change
~~rate (QTc)~~ prolongation or that is a known strong CYP inhibitor.	or that is a known strong CYP inhibitor.	
Prohibited medications that are associated with QT~~c~~ prolongation are listed in Appendix H, ~~Table 10~~ Table 11. ~~Prohibited antipsychotic drugs are listed in Appendix H, Table 11.~~	Prohibited medications that are associated with QT prolongation are listed in Appendix H, Table 11.	Prohibited antipsychotic drugs table has been deleted.
5.7.Procedures for Monitoring Patient Compliance		
A check of compliance with IMP intake will be performed during each in-clinic visit after the used IMP has been ~~dispensed~~returned, and IMP accountability records will be completed. At week 3, IMP administration compliance can be calculated only for weeks 1 and 2, as the last kit at week 3 is returned to the patient so that the patient can complete the week 3 dosing for that evening.	A check of compliance with IMP intake will be performed during each in-clinic visit after the used IMP has been returned, and IMP accountability records will be completed. At week 3, IMP administration compliance can be calculated only for weeks 1 and 2, as the last kit at week 3 is returned to the patient so that the patient can complete the week 3 dosing for that evening.	Clarified calculation of IMP compliance
5.8 Temporary Discontinuation of Investigational Medicinal Product		
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~~7 days after the change. If a dose suspension occurs before a scheduled clinic visit, an unscheduled visit should be scheduled as soon as possible so that efficacy evaluations can be performed at least ~~5~~7 days after the change.	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 7 days after the change. If a dose suspension occurs before a scheduled clinic visit, an unscheduled visit should be scheduled as soon as possible so that efficacy evaluations can be performed at least 7 days after the change.	Clarified evaluations can occur 7 days after a dose reduction or suspension
If a patient's serum potassium or magnesium level falls below the lower limit of normal, IMP ~~must~~ should be suspended.	If a patient's serum potassium or magnesium level falls below the lower limit of normal, IMP should be suspended.	Clarification
5.9. Randomization and Blinding		
The iDMC will perform ~~an~~one unblinded non-binding IA for futility, another unblinded IA for futility and sample size reassessment and safety monitoring throughout the study. An iDMC charter will be developed for the interim analyses, and the procedures to ensure the integrity of the study will be provided in the charter (see Section 5.10.3 for more details).	The iDMC will perform one unblinded non-binding IA for futility, another unblinded IA for futility and sample size reassessment and safety monitoring throughout the study. An iDMC charter will be developed for the interim analyses, and the procedures to ensure the integrity of the study will be provided in the charter (see Section 5.10.3 for more details).	Text updated to account for the second interim analysis

Protocol text with changes shown	New wording	Reason/justification for change
See new wording column	Patients re-entering the study will be manually assigned to their initial treatment group by the RTSM unblinded vendor. Blinding will be maintained for the patient, investigator, and sponsor as described above; the only information that will be available is that the patient was assigned to the same treatment group previously.	Guidance provided on how to handle blinding for patients who re-enter the study
5.10.3. Independent Data Monitoring Committee		
See new wording column	When approximately 50 patients have completed the study (including follow-up), the iDMC will perform an unblinded non-binding IA for futility based on centrally read MD-CRS part II total score.	Text added for the addition of the second interim analysis
The iDMC charter will be developed for the IAs, and the procedures to ensure the integrity of the study will be provided in the charter.	The iDMC charter will be developed for the IAs, and the procedures to ensure the integrity of the study will be provided in the charter.	Text updated to account for the second interim analysis
6. ASSESSMENT OF EFFICACY		
See new wording column	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 PGI-I. 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-30080 RECLAIM-DCP: Order of scales administration/completion document). At all relevant visits where collected, PGI-I and CaGI-I are to be completed before all other investigator-rated 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.	Stated the efficacy assessments and clarified the timing of those assessments
6.1. Primary Efficacy Measure		
The MD-CRS part II will be administered by the investigational center physician, or other appropriately trained study team member, and video recorded at screening,	The MD-CRS part II will be administered by the investigational center physician, or other appropriately trained study team member, and video recorded at	Clarified who can administered the MD-CRS

Protocol text with changes shown	New wording	Reason/justification for change
baseline, week 9, week 12, week 15/ET, and week 16/EOS visits.	screening, baseline, week 9, week 12, week 15/ET, and week 16/EOS visits.	
See new wording column	The MD-CRS has been updated to version 2 with changes to the scoring language. This version should be used when available. However, a patient will complete all study visits using the same version.	Clarified the version of the MD-CRS
• Central reading (baseline, week 9, week 12, week 15/ET, and week 16/EOS): Video review of MD CRS part II will be assessed periodically in a blinded manner (ie, visit, investigator site rating, and other study related information) by a central review board.	• Central reading (baseline, week 9, week 12, week 15/ET, and week 16/EOS): Video review of MD CRS part II will be assessed periodically in a blinded manner (ie, visit, investigator site rating, and other study related information) by a central review board.	Clarification
6.2.1. Movement Disorder-Childhood Rating Scale Part I Total Score		
See new wording column	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.	Clarified who can administered the MD-CRS
6.2.2. Caregiver Global Impression of Improvement Scale		
The CaGI-I is to be completed ~~assessed~~ before all other investigator-rated scales during visits where CaGI-I is collected (Table 3).	The CaGI-I is to be completed before all other investigator-rated scales during visits where CaGI-I is collected (Table 3).	Clarification
6.3.2. Unified Huntington's Disease Rating Scale-Total Motor Score		
The UHDRS-TMS is administered at baseline, week 9, week 12, and week 15/ET visits and will be rated by the investigator.	The UHDRS-TMS is administered at baseline, week 9, week 12, and week 15/ET visits and will be rated by the investigator.	Clarified who can rate the UHDRS-TMS
6.3.4. Unified Huntington's Disease Rating Scale-Total Maximal Dystonia		
See new wording column	When rating dystonia (question #11) buccal-oral-lingual and facial dystonia (blepharospasm, jaw opening and closing) should be included in the assessment of the truncal region.	Clarified what should be part of the assessment for dystonia
6.3.7. Patient Global Impression of Improvement Scale		
The PGI-I is to be completed~~assessed~~ before all other investigator-rated scales during visits where PGI-I is collected (Table 3).	The PGI-I is to be completed before all other investigator-rated scales during visits where PGI-I is collected (Table 3).	Clarification

Protocol text with changes shown	New wording	Reason/justification for change
7. ASSESSMENT OF SAFETY		
See new wording column	The investigator should review all scales and questionnaires in a timely manner for any potential reporting of adverse events and document this review accordingly.	Guidance provided on timing of the assessments of all scales and questionnaires
7.1.2. Recording and Reporting of Adverse Events		
The follow-up period of recording of adverse events is defined as 2 weeks after the last dose of IMP ~~for patients who will not roll over into~~ or up to baseline/day 1 in the open-label ~~safety~~ extension ~~study~~ Study TV50717-CNS-30081 (whichever comes first) or 2 weeks after the ET visit for patients who terminate early from the ~~study, or the date of enrollment in the open-label extension (OLE) study TV50717-CNS-30081 for patients rolling over to the OLE~~ study.	The follow-up period of recording of adverse events is defined as 2 weeks after the last dose of IMP or up to baseline/day 1 in the open-label extension Study TV50717-CNS-30081 (whichever comes first) or 2 weeks after the ET visit for patients who terminate early from the study.	Clarified the timing of when a patient can enter Study TV50717-CNS-30081
See new wording column	To enable the assessment of the potential relationship of an adverse event and plasma concentration of IMP and metabolites, blood samples will be collected based on the scenarios described in Table 9.	Additional guidance provided on how to handle blood samples for plasma concentration of IMP and metabolites
7.2. Safety Rating Scales		
See new wording column	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.	Guidance provided on timing of the assessments of all scales and questionnaires
7.2.1. Children's Columbia-Suicide Severity Rating Scale		
For children over 13 years of age, parent/~~legal guardian~~ legally accepted representative involvement is strongly encouraged. Questions should be directed to the child, but the caregiver parent/~~legal guardian~~ legally accepted representative should be encouraged to add relevant information.	For children over 13 years of age, parent/legally accepted representative involvement is strongly encouraged. Questions should be directed to the child, but the caregiver parent/legally accepted representative should be encouraged to add relevant information.	Clarified one of the terms for caregiver for patients who are minors

Protocol text with changes shown	New wording	Reason/justification for change
7.3. Pregnancy		
See new wording column	Note: Female partners' pregnancies of male participants are not required to be proactively monitored.	Clarification
7.5.1. Serum Chemistry, Hematology, and Urinalysis		
See new wording column	Laboratory tests performed at screening may be repeated to determine patient eligibility.	Text added to allow for repeat testing for study entry
7.5.2.1. Beta-Human Chorionic Gonadotropin Tests		
β-HCG tests in urine will be performed for all female patients aged 12 years or older of childbearing potential at baseline and other in-clinic visits as detailed in Table 3.	β-HCG tests in urine will be performed for all female patients aged 12 years or older of childbearing potential at baseline and other in-clinic visits as detailed in Table 3.	Clarified when pregnancy tests should be performed
7.5.2.2. Urine Drug Screen		
See new wording column	A urine drug screen performed at screening may be repeated to determine patient eligibility.	Text added to allow for repeat testing for study entry
If a given parameter cannot be tested using urine, or if the investigator considers additional testing is needed, an alternative matrix (eg, serum) may be considered acceptable. Such tests may be performed locally.	If a given parameter cannot be tested using urine, or if the investigator considers additional testing is needed, an alternative matrix (eg, serum) may be considered acceptable. Such tests may be performed locally.	Clarification on the possible additional testing that may be considered upon conducting the urine drug screen
See new wording column	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 or 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) and if the dosing has been stable for at least 4 weeks before screening and no changes to dose or frequency are anticipated during the course of the study. Such cases should be discussed with the medical monitor. Patients who either are using these medications or have a positive drug screen for these substances or derivatives should be submitted to the medical monitor for consideration of participation in this study.	Clarification on the possible exceptions that may be considered upon conducting the urine drug screen

Protocol text with changes shown	New wording	Reason/justification for change
	Patients with a substance use disorder are excluded from this clinical trial. However, if per the investigator's judgment, a patient does not meet the criteria for substance use disorder, a positive drug screen result 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.	
7.7. Vital Signs		
(The same position and arm or leg should be used each time vital signs are measured for a given patient.)	(The same position and arm or leg should be used each time vital signs are measured for a given patient.)	Specified the leg could be used for vital sign measurement
See new wording column	For patients who find standing difficult or do not allow for a reliable blood pressure and pulse measurement, alternative methods to collect orthostatic blood pressure and pulse should be discussed with the medical monitor.	Clarified that alternative methods for assessing vital signs can be discussed with the medical monitor
7.8. Electrocardiography		
See new wording column	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.	Clarified screening ECGs should be reviewed for eligibility
If a post-baseline QTcF value >500 msec or change from ~~baseline~~screening >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of ~~the 2~~ these 3 post-screening QTcF values to the pre-treatment QTcF values ~~(baseline and screening) to the average of the 3 post-baseline QTcF values~~ at screening. The IMP must be stopped for any confirmed post-baseline QTcF average value >500 msec or average increase from ~~baseline~~ screening >60 msec.	If a post-baseline QTcF value >500 msec or change from screening >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of these 3 post-screening QTcF values to the pre-treatment QTcF values at screening. The IMP must be stopped for any confirmed post-baseline QTcF average value >500 msec or average increase from screening >60 msec.	Clarification when and how change in QTcF would require study discontinuation
See new wording column	Note: Abnormal ECG results at week 3 and week 7 may result in patient withdrawal from the study as detailed in Section 4.3.	Cross-reference added for possibility of patient withdrawal due to abnormal ECG results

Protocol text with changes shown	New wording	Reason/justification for change
7.12. Concomitant Medication or Treatment		
Parents/patients 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 if there is any change in current medications, including over-the-counter medications. Any new prescribed/administered medication and/or any change in current prescribed/administered medication should be reviewed with the investigator.	Parents/patients 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 if there is any change in current medications, including over-the-counter medications. Any new prescribed/administered medication and/or any change in current prescribed/administered medication should be reviewed with the investigator.	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
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 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 with a substance use disorder ~~(by Diagnostic and Statistical Manual of Mental Disorders, 5th edition, criteria~~) are excluded from this clinical trial.	Patients with a substance use disorder are excluded from this clinical trial.	
See new wording column	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 and should be discussed with the medical monitor. If the wellbeing of the patient and the urgency of the clinical decision do not allow discussion with the medical monitor prior to the medication change, the investigator should notify the medical monitor in a timely manner following this decision.	
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~~e~~ prolongation or that is a known strong CYP2D6 inhibitor. Prohibited medications that are associated with QT~~e~~ prolongation are listed in Appendix H, ~~Table 10~~ Table 11~~, while prohibited antipsychotic drugs are listed in Appendix H, Table11~~.	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 prolongation or that is a known strong CYP2D6 inhibitor. Prohibited medications that are associated with QT prolongation are listed in Appendix H, Table 11.	Prohibited antipsychotic drugs table has been deleted

Protocol text with changes shown	New wording	Reason/justification for change
8.1. Pharmacokinetic Assessment		
See new wording column	[redacted]	[redacted]
See new wording column	Table 9 (Blood Sampling Scenarios) has been added	
9.1. Sample Size and Power Considerations		
Simulations for the study, including the IA for futility and sample size re-estimation, and the corresponding statistical methods to control the Type I error rate were performed. The overall power ~~of~~was approximately ~~90~~83% under the initial assumptions, and the overall Type I error rate of less than 0.025 for the primary analysis ~~were~~was confirmed. Further simulations were performed to evaluate the power and additional operating characteristics of the study under different assumptions of the effect size.	Simulations for the study, including the IA for futility and sample size re-estimation, and the corresponding statistical methods to control the Type I error rate were performed. The overall power was approximately 83% under the initial assumptions, and the overall Type I error rate of less than 0.025 for the primary analysis was confirmed. Further simulations were performed to evaluate the power and additional operating characteristics of the study under different assumptions of the effect size.	Text updated to account for the second interim analysis
9.2.1. Intent-to-Treat Analysis Set		
See new wording column	For patients who discontinue the study and re-enter it (repeating the study from baseline), only the data from the repeated participation will be included in the ITT analysis set.	Clarification for patients who re-enter the study
9.2.3. Safety Analysis Set		
See new wording column	Rules for handling safety data for patients who discontinue the study and re-enter it will be provided in the SAP.	Clarification for patients who re-enter the study

Protocol text with changes shown	New wording	Reason/justification for change
9.3.1. Handling Withdrawals and Missing Data		
The following cases will be considered as MNAR: • early terminations related to tolerability • treatment-related adverse events • <u>early terminations related to</u> lack of efficacy The following cases will be considered as MAR: • intermittent missing data • early termination for patients who are lost to follow-up • <u>early terminations due to COVID-19</u>	The following cases will be considered as MNAR: • early terminations related to tolerability • treatment-related adverse events • early terminations related to lack of efficacy The following cases will be considered as MAR: • intermittent missing data • early termination for patients who are lost to follow-up • early terminations due to COVID-19	Text added to provide additional clarity around the cases for missing data
For all other cases<u>, and for cases classified as above,</u> classification as MAR/MNAR will be done<u>/revisited</u> in a blinded manner on a case-by-case basis prior to the IA for futility<u>, the IA for futility</u> and sample size reassessment and prior to database lock for final analysis.	For all other cases, and for cases classified as above, classification as MAR/MNAR will be done/revisited in a blinded manner on a case-by-case basis prior to the IA for futility, the IA for futility and sample size reassessment and prior to database lock for final analysis.	Text added to provide additional clarity around the cases for missing data
9.4.1. Patient Disposition		
Data from patients screened; patients screened but not randomized (and reason not randomized); patients who are randomized; patients randomized but not treated ~~(and reason not treated)~~; <u>patients re-randomized;</u> patients in the ITT, mITT, safety, and PP analysis sets; patients who complete the treatment period; patients who complete the EOS visit; patients who intend to enroll into the open-label extension study; patients who do not intend to be enrolled into the open-label extension study ~~(and reason for not enrolling)~~; and patients who withdraw from the study will be summarized using descriptive statistics.	Data from patients screened; patients screened but not randomized (and reason not randomized); patients who are randomized; patients randomized but not treated; patients re-randomized; patients in the ITT, mITT, safety, and PP analysis sets; patients who complete the treatment period; patients who complete the EOS visit; patients who intend to enroll into the open-label extension study; patients who do not intend to be enrolled into the open-label extension study; and patients who withdraw from the study will be summarized using descriptive statistics.	Clarified that the reasons patient were not treated or not enrolled would not be collected and added re-randomized patients
9.5.5. Other Efficacy Endpoints		
Other efficacy endpoints (change from baseline to week 15/proportion at week 15; TEV-50717 versus placebo) are the following: • <u>MD-CRS part I total score (general assessment, physician rated)</u> • <u>MD-CRS part II total score (general assessment,</u>	Other efficacy endpoints (change from baseline to week 15/proportion at week 15; TEV-50717 versus placebo) are the following: • MD-CRS part I total score (general assessment, physician rated) • MD-CRS part II total score (general assessment,	Text added to provide additional clarity around the MD-CRS

Protocol text with changes shown	New wording	Reason/justification for change
physician rated) • MD-CRS Global Index (calculated from MD-CRS parts I and II total scores) • UHDRS-TMS (physician rated) • UHDRS-TMC (physician rated) • UHDRS-TMD (physician rated)	physician rated) • MD-CRS Global Index (calculated from MD-CRS parts I and II total scores) • UHDRS-TMS (physician rated) • UHDRS-TMC (physician rated) • UHDRS-TMD (physician rated)	
9.7. Planned Interim Analysis		
Therefore, ~~an~~ IAs for futility and sample size re-estimation ~~is~~ are planned.	Therefore, IAs for futility and sample size re-estimation are planned.	Change made to account for the multiple IA
See new wording column	When approximately 50 patients have completed the study (including follow-up), an iDMC will perform an unblinded non-binding IA for futility based on centrally read MD-CRS part II total score.	Text updated to account for the second interim analysis
The rules for futility recommendation in the first IA, and the futility and sample size re-estimation in the second IA (eg, definition of the promising zone) will be included in the iDMC charter and the SAP. The iDMC charter will also provide the wording that will be used to communicate the iDMC recommendation. The SAP will be finalized before the IAs will be performed.	The rules for futility recommendation in the 1st IA, and the futility and sample size re-estimation in the 2nd IA (eg, definition of the promising zone) will be included in the iDMC charter and the SAP. The iDMC charter will also provide the wording that will be used to communicate the iDMC recommendation. The SAP will be finalized before the IAs will be performed.	Text updated to account for the second interim analysis
9.8. Safety Endpoints and Analysis		
Changes in laboratory, ECG, and vital signs measurements data will be summarized descriptively. ~~All~~ECG and vital signs values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.	Changes in laboratory, ECG, and vital signs measurements data will be summarized descriptively. ECG and vital signs values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.	Change made to clarify which data should be compared with predefined criteria
REFERENCES		
See new wording column	National Institute of Neurological Disorders 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.	

Protocol text with changes shown	New wording	Reason/justification for change
Posner K, Brown G, Stanley B, Brent, D, Yershova K, Oquendo M, et al. The Columbia–Suicide Severity Rating Scale: ~~Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. American Journal of~~initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266-77.	Posner K, Brown G, Stanley B, Brent, D, Yershova K, Oquendo M, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266-77.	
APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Row: Scales and Central Rater for MD-CRS Column: ~~Bracket Global LLC~~ ~~575 East Swedesford Road~~ ~~Suite 200~~ ~~Wayne~~Signant Health 785 Arbor Way Blue Bell, PA ~~19087~~ 19422 Tel: [redacted]	Row: Scales and Central Rater for MD-CRS Column: Signant Health 785 Arbor Way Blue Bell, PA 19422 Tel: [redacted]	Administrative change
APPENDIX B. INDEPENDENT DATA MONITORING COMMITTEE		
When approximately ~~90~~50 patients have completed the study (including follow-up), an independent Data Monitoring Committee (iDMC) will perform an unblinded non-binding interim analysis (IA) for futility ~~and sample size re-estimation~~ based on centrally read Movement Disorder-Childhood Rating Scale part II~~.~~ (MD-CRS part II) total score. Based on the results of the ~~interim analysis~~IA, the study may be stopped.	When approximately 50 patients have completed the study (including follow-up), an independent Data Monitoring Committee (iDMC) will perform an unblinded non-binding interim analysis (IA) for futility based on centrally read Movement Disorder-Childhood Rating Scale part II (MD-CRS part II) total score. Based on the results of the IA, the study may be stopped.	
When approximately 90 patients have completed the study (including follow-up), an iDMC will perform an unblinded IA for futility and sample size re-estimation based on centrally read MD CRS part II. Based on the results of the IA, the study may be stopped or the sample size may be kept as planned (approximately 185 total patients) or increased (up to approximately 230 total patients).	When approximately 90 patients have completed the study (including follow-up), an iDMC will perform an unblinded IA for futility and sample size re-estimation based on centrally read MD CRS part II. Based on the results of the IA, the study may be stopped or the sample size may be kept as planned (approximately 185 total patients) or increased (up to approximately 230 total patients).	

Protocol text with changes shown	New wording	Reason/justification for change
APPENDIX C. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
1. Procedures for Screening (Day -31)		
• patients, parent(s)/~~legal guardian~~legally accepted representative(s), and caregivers must provide their respective written informed consent and/or assent (as appropriate) before any study related procedures are performed.	• patients, parent(s)/legally accepted representative(s), and caregivers must provide their respective written informed consent and/or assent (as appropriate) before any study related procedures are performed.	Study procedures and assessments have been updated for consistency with changes made to the protocol body and Table 3. This justification applies to all changes indicated within Appendix C.
– use of patient's study videos for future analysis of gait digital markers and release of patient's study videos for use in publications or educational presentations	– use of patient's study videos for future analysis of gait digital markers and release of patient's study videos for use in publications or educational presentations	
• clinical laboratory tests (chemistry, hematology, and urinalysis); these tests may be repeated to determine patient eligibility • urine drug screen; these tests may be repeated to determine patient eligibility	• clinical laboratory tests (chemistry, hematology, and urinalysis); these tests may be repeated to determine patient eligibility • urine drug screen; these tests may be repeated to determine patient eligibility	
See new wording column	• contact RTMS	
2. Procedures Before Administration of Investigational Medicinal Product (Baseline [Day 1±0 days])		
See new wording column	The investigator should review all available data to determine patient eligibility before randomizing to the study.	
• assignment of randomization/treatment numbers after patient eligibility is confirmed based on all available visit assessments, and entry into case report form (CRF)	• assignment of randomization/treatment numbers after patient eligibility is confirmed based on all available visit assessments, and entry into case report form (CRF)	

Protocol text with changes shown	New wording	Reason/justification for change
3. Procedures During Administration of Investigational Medicinal Product (Double-Blind Treatment Period Inclusive of Titration Period).		
a. Week 1 (day 7+1 day), week 2 (day 14±3 days total from baseline), week 4 (day 28±3 days total from baseline), week 5 (day 35±3 days total from baseline), and week 6 (day 42±3 days total from baseline)		
See new wording column	• contact RTMS	
b. Week 3 (day 21±3 days total from baseline) and week 7 (day 49±3 days total from baseline)		
The following procedures and assessments will be performed at weeks 3 and 7: • Caregiver Global Impression of Improvement (CaGI-I) (global, caregiver rated). The CaGI-I is to be completed ~~assessed~~ before all other investigator-rated scales during visits where CaGI-I is collected. • Patient Global Impression of Improvement Scale (PGI-I) (global, patient/caregiver). The PGI-I is to be completed ~~assessed~~ before all other investigator-rated scales during visits where PGI-I is collected.	The following procedures and assessments will be performed at weeks 3 and 7: • Caregiver Global Impression of Improvement (CaGI-I) (global, caregiver rated). The CaGI-I is to be completed before all other investigator-rated scales during visits where CaGI-I is collected. • Patient Global Impression of Improvement Scale (PGI-I) (global, patient/caregiver). The PGI-I is to be completed before all other investigator-rated scales during visits where PGI-I is collected.	
• dispense/collect IMP During the week 3 visit, the last dose bottle is to be returned to the patient in order to take 1 last tablet in the evening to complete the week 3 dosing for that day. Refer to the pharmacy manual for further details.	• dispense/collect IMP During the week 3 visit, the last dose bottle is to be returned to the patient in order to take 1 last tablet in the evening to complete the week 3 dosing for that day. Refer to the pharmacy manual for further details.	
See new wording column	• contact RTMS	
4. Procedures During Administration of Investigational Medicinal Product (Maintenance Period)		
a. Week 9 (day 63±3 days total from baseline) and week 12 (day 84±3 days total from baseline)		
The following was deleted: ~~• urine pregnancy test~~		
See new wording column	• contact RTMS	
b. Week 15 (day 105±3 days total from baseline) or early termination (ET)		
See new wording column	• contact RTMS	

Protocol text with changes shown	New wording	Reason/justification for change
6. Unscheduled Visits		
See new wording column	[redacted]	
APPENDIX D. QUALITY CONTROL AND QUALITY ASSURANCE		
Audit and Inspection		
See new wording column	For COVID-19 updates, refer to Appendix M.	Updated to cross-reference the addition to Appendix M
APPENDIX E. ETHICS		
See new wording column	Patients who started the study as minors and reached the age of majority during the study should sign the adult ICF.	Added text for clarification
APPENDIX H. LIST OF ALLOWED AND PROHIBITED MEDICATIONS		
Prohibited medications that are associated with QTc prolongation are listed in ~~Table 10~~Table 11~~, whereas prohibited antipsychotic drugs are listed in Table 11~~.	Prohibited medications that are associated with QTc prolongation are listed in Table 11.	Prohibited antipsychotic drugs table has been deleted.
Table ~~9~~10: Allowed Medications		
See new wording column	Table 10 has been revised as described below: – added text to include dose was "and 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 10 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 ~~10~~11: Prohibited QTc Prolonging Drugs		
See new wording column	Hydroxychloroquine was added as a new prohibited drug. The following description was also added: Hydroxychloroquine is contraindicated in this trial due to the risk of QT prolongation and should be considered as not	Hydroxychloroquine was added as a new prohibited drug.

Protocol text with changes shown	New wording	Reason/justification for change
	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.	
Table 11: Prohibited Antipsychotic Drugs		
Table deleted		Prohibited antipsychotic drugs table has been deleted.
APPENDIX I. TOTAL BLOOD VOLUME		
Table 12: Total Blood Volumes	**Table 12: Total Blood Volumes**	Table number updated
See new wording column	[redacted]	[redacted]
APPENDIX K. DATA MANAGEMENT AND RECORD KEEPING		
Data Collection		
If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, and electronic patient-reported outcome tablet or phone), these data will be sent to the investigational center…	If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, and electronic patient-reported outcome tablet or phone), these data will be sent to the investigational center…	Added another device for possible other sources
APPENDIX M. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19		
Section 3.5. Schedule of Study Procedures and Assessments		
It will further allow a visual confirmation of a patient's condition using ~~FaceTime®~~ non-recording live video and assessment of any new adverse events, as possible, depending on patient cooperation and the communication platform being in good working order.	It will further allow a visual confirmation of a patient's condition using non-recording live video and assessment of any new adverse events, as possible, depending on patient cooperation and the communication platform being in good working order.	Clarification

Protocol text with changes shown	New wording	Reason/justification for change
The remote visit will not allow for measuring vital signs or obtaining an electrocardiogram (ECG) or urine beta chorionic gonadotropin (β-HCG) test, unless a home nursing vendor is at the patient's home to provide that service where available.	The remote visit will not allow for measuring vital signs or obtaining an electrocardiogram (ECG) or urine beta chorionic gonadotropin (β-HCG) test, unless a home nursing vendor is at the patient's home to provide that service where available.	Clarification
All shipping arrangements will be the site's responsibility and will occur between site and patient or as a direct-to-patient shipment from the site to patient coordinated by the sponsor's third party shipping vendor, where available, and according to local practices and regulations.	All shipping arrangements will be the site's responsibility and will occur between site and patient or as a direct-to-patient shipment from the site to patient coordinated by the sponsor's third party shipping vendor, where available, and according to local practices and regulations.	Clarification
See new wording column	**Section 4.5. Rescreening** Patients who screen fail or terminate early from the study due to emergency circumstances (such as coronavirus disease 2019 [COVID-19] restrictions) may be allowed to re-screen/re-enter (respectively) the study at a later date, depending on the circumstances. Each case should be referred to the medical monitor and approved in advance. Patients re-entering the study will be manually assigned to their initial treatment group. Patients will have to redo the entire study from the start, aside from the blinded CYP2D6 genotyping; these results will carried over from the first participation.	Clarification for possible re-entry into the study in an emergency situation
See new wording column	**Section 5.9. Randomization and Blinding** Patients re-entering the study will be manually assigned to their initial treatment group by the RTSM unblinded vendor. Blinding will be maintained for the patient, investigator, and sponsor as described above; the only information that will be available is that the patient was assigned to the same treatment group as previously.	Clarification for possible re-entry into the study in an emergency situation
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), patients will be allowed to obtain vital signs and ECGs using local clinics	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 will be allowed to obtain vital signs and ECGs using local	

Protocol text with changes shown	New wording	Reason/justification for change
(primary health care provider) or home nursing service, where available.	clinics (primary health care provider) or home nursing service, where available	
Appendix D. Quality Control and Quality Assurance		
Study Monitoring In case of an emergency situation (eg, the COVID-19 pandemic), where study monitors may not be able to access the investigational centers for on-site visits ~~in a timely manner. A remote monitoring risk mitigation plan~~, sites will be ~~utilized for sites where on-site monitoring visits are not permitted. Details~~ monitored remotely where allowed and in accordance with the local regulations. Additional details are provided in the monitoring plan.	**Study Monitoring** In case of an emergency situation (eg, the COVID-19 pandemic), where study monitors may not be able to access the investigational centers for on-site visits, sites will be monitored remotely where allowed and in accordance with the local regulations. Additional details are provided in the monitoring plan.	Minor clarification for remote monitoring considerations in an emergency situation
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.	Minor clarification for remote auditing considerations in an emergency situation

16.4. Amendment 03 Dated 08 June 2020

The primary reason for this amendment is to provide the management of coronavirus disease 2019 (COVID-19) pandemic-related operational updates as detailed in a new appendix (Appendix M). Administrative changes have been applied, including updating the Table of Contents.

Original text with changes shown	New wording	Reason/Justification for change
3.1. General Study Design and Study Schematic Diagram		
See New Wording Column	For coronavirus disease 2019 (COVID-19) updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M
3.5. Schedule of Study Procedures and Assessments		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M
4.3. Withdrawal Criteria and Procedures for the Patient		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M
6. ASSESSMENT OF EFFICACY		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M
7. ASSESSMENT OF SAFETY		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M
7.5.2.1. Beta-Human Chorionic Gonadotropin Tests		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M
7.5.2.2. Urine Drug Screen		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M
9. Statistics		
See New Wording Column	For COVID-19 updates, refer to Appendix M.	Updated sections 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 sections to cross-reference the addition of Appendix M
Appendix D. Quality Control and Quality Assurance		
See New Wording Column	For coronavirus disease 2019 (COVID-19) updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M
Appendix E. Ethics		
See New Wording Column	For coronavirus disease 2019 (COVID-19) updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M

Original text with changes shown	New wording	Reason/Justification for change
Appendix H. List Of Allowed And Prohibited Medications		
See New Wording Column	For coronavirus disease 2019 (COVID-19) updates, refer to Appendix M.	Updated sections to cross-reference the addition of Appendix M
Appendix M. Management of Study Activities During COVID-19		
New appendix and text	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.

16.5. Amendment 02 Dated 17 October 2019

The primary reason for this amendment is to add new secondary endpoints, provide additional withdrawal criteria, and to clarify the inclusion/exclusion criteria.

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

Other minor or editorial 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.

Original text with changes shown	New wording	Reason/Justification for change
Synopsis and throughout the protocol		
~~Parent/~~caregiver	caregiver	Clarification
Caregiver~~/adult~~	caregiver	
Synopsis [Regions Planned]		
North America, Asia, and ~~the~~ Europe~~an Union~~	North America, Asia, and Europe	Clarification
Synopsis [General Study Design] (Other sections affected by anyone of these changes: 3.1)		
This is a Phase 3, 21-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of TEV-50717 administered as oral tablets at a starting dose of 6 mg once daily in patients (age 6 through 18 years) with DCP with predominant choreiform movement disorder, who have had CP symptoms, of a non-progressive nature, since infancy (≤2 years of age). "Predominant" in this instance indicates that the choreiform movement disorder is the main cause of impairment or distress.	This is a Phase 3, 21-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of TEV-50717 administered as oral tablets at a starting dose of 6 mg once daily in patients (age 6 through 18 years) with DCP with predominant choreiform movement disorder, who have had CP symptoms, of a non-progressive nature, since infancy (≤2 years of age). "Predominant" in this instance indicates that the choreiform movement disorder is the main cause of impairment or distress.	Clarification
Synopsis [General Study Design] (Other sections affected by anyone of 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 responsibility as acaregiver. The parent or legal guardian only has to sign the parent/legal guardian informed consent form (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 responsibility as a caregiver. The parent or legal guardian only has to sign the parent/legal guardian informed consent form (ICF) and not the caregiver ICF. For adult patients, a caregiver must be appointed by the	Clarification

Original text with changes shown	New wording	Reason/Justification for change
patient; this can be the parent, a legal guardian, 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 child's health, or where "parent/legal guardian" is specifically indicated in the protocol.	patient; this can be the parent, a legal guardian, 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 the IMP, or withdrawal from the study for any reason. To further clarify, the caregiver is not allowed to make decisions on child's health or where "parent/legal guardian" is specifically indicated in the protocol.	
IMP will be titrated during the double-blind treatment period starting with 6 mg of TEV-50717 or matching placebo IMP in the morning of days 2 and 3~~, followed by~~ Patients with a body weight ≥40 kg/88 lbs will further dose in the evening ~~administration~~ starting on day 3 and for the remainder of the first week ~~(if body weight is ≥40 kg/88 lbs)~~.	IMP will be titrated during the double-blind treatment period starting with 6 mg of TEV-50717 or matching placebo IMP in the morning of days 2 and 3. Patients with a body weight ≥40 kg/88 lbs will further dose in the evening starting on day 3 and for the remainder of the first week.	Clarification
Synopsis [Screening Period]		
After written informed consent/~~(and written~~ assent ~~and/or co-consent for patients 14 years of age and older~~, as appropriate~~,)~~ is obtained, ...	After written informed consent/assent, as appropriate, is obtained, ...	Clarification
...The EAB will also confirm, based on video recordings, that choreiform is clinically the predominant movement disorder of the patient's DCP. EAB assessment results will be available to the investigator prior to baseline and randomization. ~~At all other visits, T~~the MD-CRS part II will be administered by the investigational center physician and video review, for central-blinded reading. In this study, the MD-CRS part II will be scored only based on chorea.	...The EAB will also confirm, based on video recordings, that choreiform is clinically the predominant movement disorder of the patient's DCP. EAB assessment results will be available to the investigator prior to baseline and randomization. The MD-CRS part II will be administered by the investigational center physician and video review, for central-blinded reading. In this study, the MD-CRS part II will be scored only based on chorea.	Clarification
Synopsis [Titration Period]		
Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer. At the baseline visit, a	Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer. At the baseline visit, a	Clarification

Original text with changes shown	New wording	Reason/Justification for change
telephone for non-recording live video will be provided to the patient and caregiver. Patients and their caregiver~~/adult~~ will interact weekly with the investigator/staff, either by telephone contact (with non-recording live video) ...	telephone for non-recording live video will be provided to the patient and caregiver. Patients and their caregiver will interact weekly with the investigator/staff, either by telephone contact (with non-recording live video)	
Synopsis [Washout Period] (Other sections affected by anyone of these changes: Synopsis [Plan for Treatment or Care], 3.1, and 5.4)		
Patients who complete treatment, but choose not to participate ~~not participating~~ in the open-label safety extension Study TV50717-CNS-30081 will be contacted ~~have a follow-up telephone contact~~ for a safety evaluation call occurring~~1 week after the end of the washout period (~~2 weeks after their last dose of IMP ~~[week 17])~~.	Patients who complete treatment, but choose not to participate in the open-label safety extension Study TV50717-CNS-30081 will be contacted for a safety evaluation call occurring 2 weeks after their last dose of IMP.	Clarification
Synopsis [Washout Period] (Other sections affected by anyone of these changes: 3.1)		
All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after ~~their last dose of IMP~~ET; evaluations will be as described for week 17.	All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after ET; evaluations will be as described for week 17.	Change originally included in Letter of Clarification #5 (Section 16.2).
Synopsis [Inclusion Criteria] (Other sections affected by anyone of these changes: 4.1)		
5. Patient has an MD-CRS part II total score of ≥10 at the baseline visit, based on investigator scoring of chorea. 7. Choreiform is the predominant (ie, the main cause of impairment or distress) movement disorder as assessed at screening. 12. ~~Patient and caregiver/adult provided written informed consent according to local regulations (eg, for patients/adolescents, the patient has provided written assent and/or co-consent for patients 14 years of age and older, as appropriate).~~ For a patient who is a minor, the parent(s)/legal guardian(s) provide written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide their own written informed consent (in accordance with local	5. Patient has an MD-CRS part II total score of ≥10 at the baseline visit, based on investigator scoring of chorea. 7. Choreiform is the predominant (ie, the main cause of impairment or distress) movement disorder as assessed at screening. 12. For a patient who is a minor, the parent(s)/legal guardian(s) provide written informed consent, and the patient provides assent (in accordance with local regulations). Adult patients provide their own written informed consent (in accordance with local regulations). 13. Caregivers 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	Clarification

Original text with changes shown	New wording	Reason/Justification for change
regulations). 13. Caregivers 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.	patient who is a minor.	
Synopsis [Exclusion Criteria]		
6. Patient who is currently receiving or who, in the last 4 months before screening, 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, and if they are expected to continue this stable regimen of BoNT injections for the duration of this study. The patient is expected to continue on this stable regimen of BoNT injections on a regularly scheduled interval every 3 months 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. "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. – Note: Patients who received BoNT injections	6. Patient who is currently receiving or who, in the last 4 months before screening, 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, and if they are expected to continue this stable regimen of BoNT injections for the duration of this study. The patient is expected to continue on this stable regimen of BoNT injections on a regularly scheduled interval every 3 months 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. "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. – Note: Patients who received BoNT injections	Clarification

Original text with changes shown	New wording	Reason/Justification for change
more than 4 months before screening and who do not plan to continue these injections may be considered for this study.	more than 4 months before screening and who do not plan to continue these injections may be considered for this study.	
13. Patient has evidence of diminished hepatic ~~impairment~~function, as indicated by the following:	13. Patient has evidence of diminished hepatic function, as indicated by the following:	Clarification
19. Patient has a positive urine drug screen test result (with exception of medications listed in Table 9 of Appendix H) or is unable to refrain from substance abuse throughout the study.	19. Patient has a positive urine drug screen test result (with exception of medications listed in Table 9 of Appendix H) or is unable to refrain from substance abuse throughout the study.	Clarification
1.2.2. Clinical Studies		
The clinical development plan for TEV-50717 to date includes the following: 1. ~~Six~~Nine completed Phase 1 studies in healthy adult volunteers	The clinical development plan for TEV-50717 to date includes the following: 2. Nine completed Phase 1 studies in healthy adult volunteers	Update
1.2.2. Clinical Pharmacology Studies		
~~Six~~ Nine Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers.	Nine Phase 1 clinical pharmacology studies were conducted in healthy adult volunteers.	
3.1. General Study Design		
...and assessment of sedation according to the Epworth Sleepiness Scale (for children and adolescents) (ESS) questionnaire ~~of using a telephone with non-recording live video will be made possible, and the adoption of live video to support patient/caregiver interview will then be maintained throughout the study for the evaluation of safety/tolerability and dyskinesia severity~~.	...and assessment of sedation according to the Epworth Sleepiness Scale (for children and adolescents) (ESS) questionnaire.	Clarification

Original text with changes shown	New wording	Reason/Justification for change
Figure 1:Overall Study Schematic Diagram		
		Clarification
3.2 Planned Number of Patients and Regions		
This study is planned to be conducted in approximately 70 investigational centers in North America, Asia, and ~~the~~ Europe~~an Union (EU)~~.	This study is planned to be conducted in approximately 70 investigational centers in North America, Asia, and Europe.	Clarification
Table 3: Study Procedures and Assessments		
First Column Row: Informed consent/assent ~~and/or co-consent for patients (as applicable)~~[j]	First Column Row: Informed consent/assent[j]	Clarification
d For patients who withdraw prematurely, an ET visit should be conducted as soon as possible after the last dose of IMP. All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after ~~their last dose of IMP~~ET; evaluations will be as described for week 17. j [redacted] r For females who are postmenarchal or aged ≥12 years of childbearing potential. Serum test will be administered at ~~baseline~~screening and week 15, whereas a urine test will be administered at ~~screening~~baseline and all other in-clinic visits. z ~~Parents/~~Caregivers and patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator.	d For patients who withdraw prematurely, an ET visit should be conducted as soon as possible after the last dose of IMP. All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after ET; evaluations will be as described for week 17 j [redacted] r For females who are postmenarchal or aged ≥12 years of childbearing potential. Serum test will be administered at screening and week 15, whereas a urine test will be administered at baseline and all other in-clinic visits. z Caregivers and patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator.	Clarification
4.2. Exclusion Criteria		
6. Patient who is currently receiving or who, in the last 4 months before screening, has received botulinum	6. Patient who is currently receiving or who, in the last 4 months before screening, has received botulinum	

Original text with changes shown	New wording	Reason/Justification for change
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 judgement) 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 patient is expected to continue on this stable regimen of BoNT injections on a regularly scheduled interval every 3 months 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. "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. – Note: Patients who received BoNT injections more than 4 months before screening and who do not plan to continue these injections may be considered for this study.	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 judgement) 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 patient is expected to continue on this stable regimen of BoNT injections on a regularly scheduled interval every 3 months 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. "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. – Note: Patients who received BoNT injections more than 4 months before screening and who do not plan to continue these injections may be considered for this study.	
13. Patient has evidence of diminished hepatic ~~impairment~~function, as indicated by the following:	13. Patient has evidence of diminished hepatic function, as indicated by the following:	
19. Patient has a positive urine drug screen test result (with exception of medications listed in Table 9 of Appendix H) or is unable to refrain from substance abuse throughout the study.	19. Patient has a positive urine drug screen test result (with exception of medications listed in Table 9 of Appendix H) or is unable to refrain from substance abuse throughout the study.	
4.3. Withdrawal Criteria and Procedures for the Patient		

Original text with changes shown	New wording	Reason/Justification for change
9. Patient has evidence of diminished hepatic function based on the following liver function laboratory test results: a. AST or ALT >2.5 × ULN b. ALP or total bilirubin >2 × ULN 10. Patient develops Neuroleptic Malignant Syndrome (NMS)	9. Patient has evidence of diminished hepatic function based on the following liver function laboratory test results: a. AST or ALT >2.5 × ULN b. ALP or total bilirubin >2 × ULN 10. Patient develops Neuroleptic Malignant Syndrome (NMS)	Clarification
5.5. Restrictions		
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 IMP dosing can be made. The addition of a strong CYP2D6 inhibitor is prohibited during the study.	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 IMP dosing can be made. The addition of a strong CYP2D6 inhibitor is prohibited during the study.	Clarification
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.	
Use of ~~illicit~~non-approved drugs (per protocol) is prohibited from the time of signing of the ICF and throughout study participation.	Use of non-approved drugs (per protocol) is prohibited from the time of signing of the ICF and throughout study participation.	
5.6. Prior and Concomitant Medication		
At each clinic visit after the screening visit, the investigator will ask patients and/or ~~parent(s)/~~caregiver whether ~~they or~~ the patient~~, respectively, have~~ has taken any medications (other than IMP), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit. ~~Parents~~Caregivers and patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed, including over-the-counter medications. Any prescribed medication should be reviewed with the	At each clinic visit after the screening visit, the investigator will ask patients and/or caregiver whether the patient has taken any medications (other than IMP), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit. Caregivers and patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator. Indication, dosage,	Clarification

Original text with changes shown	New wording	Reason/Justification for change
investigator. Indication, dosage, and start and end dates should be entered on the CRF.	and start and end dates should be entered on the CRF.	
5.8. Temporary Discontinuation of Investigational Medicinal Product		
If a patient's serum potassium or magnesium level falls below the lower limit of normal, IMP 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 appropriate investigation and treatment~~. IMP treatment may only be restarted once serum potassium and/or magnesium levels have normalized. ~~The p~~Patients who restart IMP treatment will follow the visit schedule as outlined in Table 3.	If a patient's serum potassium or magnesium level falls below the lower limit of normal, IMP 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. IMP treatment may only be restarted once serum potassium and/or magnesium levels have normalized. Patients who restart IMP treatment will follow the visit schedule as outlined in Table 3.	Clarification
6.1. Primary Efficacy Measure		
Assessment of MD-CRS part II items will be based solely on chorea in this study and performed as follows: • Local assessment (all time points): the investigational center physician will administer the MD-CRS part II and complete the assessment of item scores. Note: the physicians will receive training on MD-CRS scoring prior to the study. • EAB review (screening): EAB will review the MD-CRS part II at the screening visit to confirm that dyskinesia severity is aligned with the protocol criteria for inclusion into the study. The review will include determination of the predominant dyskinesia type and scoring of MD-CRS part II items. The EAB	Assessment of MD-CRS part II items will be based solely on chorea in this study and performed as follows: • Local assessment (all time points): the investigational center physician will administer the MD-CRS part II and complete the assessment of item scores. Note: the physicians will receive training on MD-CRS scoring prior to the study. • EAB review (screening): EAB will review the MD-CRS part II at the screening visit to confirm that dyskinesia severity is aligned with the protocol criteria for inclusion into the study. The review will include determination of the predominant dyskinesia type and scoring of MD-CRS part II items. The EAB	

Original text with changes shown	New wording	Reason/Justification for change
will inform the site prior to the baseline visit if there are any discrepancies between the local and central assessments, and offer to discuss with the investigator. Ultimately, it is the investigator who determines the patient's eligibility. EAB assessment of screening MD-CRS part II total score will not be included in the statistical analysis.	will inform the site prior to the baseline visit if there are any discrepancies between the local and central assessments, and offer to discuss with the investigator. Ultimately, it is the investigator who determines the patient's eligibility. EAB assessment of screening MD-CRS part II total score will not be included in the statistical analysis.	
6.3.2. Unified Huntington's Disease Rating Scale-Total Motor Score		
The Total Motor Score assessment of the UHDRS (UHDRS TMS) comprises 15 items and assesses eye movements, speech, alternating hand movements, dystonia, chorea, and gait. The UHDRS-TMS is calculated as the sum of the 31 motor assessments; each of which ranges between 0 to 4. The minimum score is 0 (absent) and the maximum score is 124~~108~~ (worst) (Huntington Study Group 1996).	The Total Motor Score assessment of the UHDRS (UHDRS TMS) comprises 15 items and assesses eye movements, speech, alternating hand movements, dystonia, chorea, and gait. The UHDRS-TMS is calculated as the sum of the 31 motor assessments; each of which ranges between 0 to 4. The minimum score is 0 (absent) and the maximum score is 124 (worst) (Huntington Study Group 1996).	
6.3.6. Pediatric Quality of Life Inventory, Cerebral Palsy Module		
The scales comprise parallel child self-report and parent proxy-report formats. ~~Child self-report includes~~ For children ages ~~5 to~~6 and 7 years~~,~~ and 8 to 12 years, ~~and 13 to 18 years. A~~ a child self-report and a parent proxy report are completed. ~~is included in reports for ages 2 to 4 years (toddler), 5 to 7 years (young child), 8 to 12 years (child), and 13 to 18 years (adolescent), and~~ The parent proxy report assesses parents' perceptions of their child's health-related quality of life (QoL). For children ages 13 to 18 years, no parent proxy report is required. The instructions ask how much of a problem each item has been during the past 1 month. A 5-point response scale is utilized across child self-report and parent proxy report as follows:	The scales comprise parallel child self-report and parent proxy-report formats. For children ages 6 and 7 years and 8 to 12 years, a child self-report and a parent proxy report are completed. The parent proxy report assesses parents' perceptions of their child's health-related quality of life (QoL). For children ages 13 to 18 years, no parent proxy report is required. The instructions ask how much of a problem each item has been during the past 1 month. A 5-point response scale is utilized across child self-report and parent proxy report as follows:	Clarification
7.1.2. Recording and Reporting of Adverse Events		
The follow-up period of recording of adverse events is defined as 2 weeks after the last dose of IMP for patients who will not roll over into the open-label safety	The follow-up period of recording of adverse events is defined as 2 weeks after the last dose of IMP for patients who will not roll over into the open-label safety	Clarification

Original text with changes shown	New wording	Reason/Justification for change
extension study or 2 weeks after the ET visit for patients who terminate early from the study, or the date of enrollment in the open label extension (OLE) study TV50717-CNS-30081 for patients rolling over to the OLE study.	extension study or 2 weeks after the ET visit for patients who terminate early from the study, or the date of enrollment in the open label extension (OLE) study TV50717-CNS-30081 for patients rolling over to the OLE study.	
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 the IMP or study procedure is made. Adverse events of patients rolling over to the OLE study TV50717-CNS-30081 will continue to be monitored as part of the OLE study.	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 the IMP or study procedure is made. Adverse events of patients rolling over to the OLE study TV50717-CNS-30081 will continue to be monitored as part of the OLE study.	Clarification
7.2.2. Child Behavior Checklist (for Ages 6-18)		
The Syndrome Scale comprises 1138 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 parent/caregiver will circle 0 if the item is not true of their child, 1 if the item is somewhat or sometimes true, and 2 if the item is very true or often true.	The Syndrome Scale comprises 113 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.	Clarification
7.4. Medication Error and Special Situations Related to the Investigational Medicinal Products		
Any administration of IMP that is not in accordance with the study protocol should be reported inon the CRF and in the patients source documents either as a violationdeviation if it the event meets the violationdeviation criteria specified in the protocol (Appendix D), or as a deviation, in the patients source documents, regardless of whether or not an adverse event occurs as a result.	Any administration of IMP that is not in accordance with the study protocol should be reported in the CRF and in the patient's source documents as a deviation if the event meets the violation criteria specified in the protocol (Appendix D), regardless of whether or not an adverse event occurs as a result.	Clarification
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	Concomitant therapy or medication usage will be monitored throughout the study according to time points detailed in Table 3. Parents/patients will be instructed	Clarification

Original text with changes shown	New wording	Reason/Justification for change
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.~~ 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.	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 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.	

Original text with changes shown	New wording	Reason/Justification for change
8.1. Pharmacokinetic Assessment		
[redacted]	[redacted]	Bolded text added for emphasis
9.10. Pharmacokinetic/Pharmacodynamic Analysis		
[redacted]	[redacted]	Clarification
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 ~~and violations~~, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.	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.	Clarification
15. REFERENCES		
AUSTEDO® (deutetrabenazine) tablets (US prescribing information). Teva Pharmaceuticals USA, Inc; 201~~7~~9. Available at: https://austedo.com/hd/pi.	AUSTEDO® (deutetrabenazine) tablets (US prescribing information). Teva Pharmaceuticals USA, Inc; 2019. Available at: https://austedo.com/hd/pi.	Clarification

Original text with changes shown	New wording	Reason/Justification for change
Xenazine: Highlights of Prescribing Information. 2018~~5~~. Available at: ~~http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021894s010lbl.pdf~~https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ac768bab-8afa-4446-bc7f-caeeffec0cda. Accessed ~~27 Oct 2015~~05 Aug 2019.	Xenazine: Highlights of Prescribing Information. 2018. Available at: https://dailymed nlm.nih.gov/dailymed/drugInfo.cfm?setid=ac768bab-8afa-4446-bc7f-caeeffec0cda. Accessed 05 Aug 2019.	
Appendix A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Sponsor's Authorized Representative: [redacted] Teva Pharmaceutical Industries, [redacted] Cell: [redacted]	**Sponsor's Authorized Representative:** [redacted] Teva Pharmaceutical Industries, [redacted] Cell: [redacted]	Clarification
Pharmacokinetic Samples Watson Pharma Pvt. Ltd. Seawoods Grand Central, Tower 2 Level-11, Wing-E, Plot No. R-1 Sector 40, Nerul, Navi Mumbai 400706 Tel: [redacted] Contact: [redacted]	**Pharmacokinetic Samples** Watson Pharma Pvt. Ltd. Seawoods Grand Central, Tower 2 Level-11, Wing-E, Plot No. R-1 Sector 40, Nerul, Navi Mumbai 400706 Tel: [redacted] Contact: [redacted]	Addition
Scales and Central Rater for MD-CRS Bracket Global LLC 575 East Swedesford Road Suite 200 Wayne, PA	**Scales and Central Rater for MD-CRS** Bracket Global LLC 575 East Swedesford Road Suite 200 Wayne, PA	Addition

Original text with changes shown	New wording	Reason/Justification for change
19087 Tel: [redacted]	19087 Tel: [redacted]	
APPENDIX C. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
patients, ~~or~~ parent(s)/~~legally acceptable representative must provide~~ legal guardian(s), and caregivers must provide their respective written informed consent~~,~~ and/or assent (as appropriate) ~~the patients must give assent (as applicable)~~ before any study related procedures are performed. Assent/consent may also be provided to 2 optional ICFs: – [redacted] – use of patient's study videos for future analysis of gait digital markers and release of patient's study videos for use in publications or educational presentations	patients, parent(s)/legal guardian(s), and caregivers must provide their respective written informed consent and/or assent (as appropriate) before any study-related procedures are performed. Assent/consent may also be provided to 2 optional ICFs: – [redacted] – use of patient's study videos for future analysis of gait digital markers and release of patient's study videos for use in publications or educational presentations	Clarification
5. Follow-Up (Weeks 16 and 17) **a. Week 16/End of Study follow-up visit (day 112±2 days total from baseline)~~, or 1 week after ET)~~**	**5. Follow-Up (Weeks 16 and 17)** **a. Week 16/End of Study follow-up visit (day 112±2 days total from baseline)**	Change originally included in Letter of Clarification #5 (Section 16.3).

Original text with changes shown	New wording	Reason/Justification for change
6. Unscheduled Visits An unscheduled visit may be performed at any time during the study at the patient's or parent's/~~legally acceptable representative's~~caregiver's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.	**6. Unscheduled Visits** An unscheduled visit may be performed at any time during the study at the patient's or parent's/caregiver's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.	Clarification
APPENDIX D. QUALITY CONTROL AND QUALITY ASSURANCE		
Protocol Amendments and Protocol Deviations~~ and Violations~~ Important Protocol Deviations~~Violations~~ 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~~violation~~. ~~P~~Important protocol deviations~~violations~~ 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 Good Clinical Practice (GCP) guidelines; noncompliance to IMP administration; and use of prohibited medications. ~~Protocol violations will be identified and recorded by investigational center personnel in the case report form (CRF).~~ All important protocol deviations~~violations~~ will be reported to the responsible IEC/IRB, as required. When an important protocol deviation~~violation~~ 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	Protocol Amendments and Protocol Deviations 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 Good Clinical Practice (GCP) guidelines; noncompliance to IMP administration; and 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	Clarification

Original text with changes shown	New wording	Reason/Justification for change
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~~violation~~. If such patient has already completed the study or has withdrawn early, no action will be taken, but the deviation~~violation~~ will be recorded.	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.	
APPENDIX F. BIRTH CONTROL METHODS AND PREGNANCY TESTING		
Females ~~(aged 12 years or older)~~ of childbearing potential are defined as the following:	**Females of childbearing potential are defined as the following:**	Clarification
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 9. Investigators are encouraged to contact the medical monitor for any questions regarding the medications listed below.	Medications that are allowed, provided that conditions outlined in the table are met, are shown in Table 9. Investigators are encouraged to contact the medical monitor for any questions regarding the medications listed below.	
Table 9: Allowed Medications		
Row: Allowed strong CYP2D6 inhibitors[a]	Row: Allowed strong CYP2D6 inhibitors[a]	Clarification
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, 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, under the guidance, supervision, or prescription of a clinician.	
Table 12: Total Blood Volumes		
Row 1 Column 4: Week 16/EOS	Row 1 Column 4: Week 16/EOS	Clarification

16.6. Letter of Clarification 06 Dated 05 August 2019

LETTER OF CLARIFICATION #6 FOR UNITED KINGDOM

Study number: TV50717-CNS-30080

Clinical Study Protocol Amendment 01: A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents, Dated 20 December 2018

IND number: 139700; NDA number: NA; EudraCT number: 2018-003742-17

05 August 2019

Dear Investigator:

The purpose of this letter of clarification is to address:

- the addition of diminished hepatic function and Neuroleptic Malignant Syndrome (NMS) as a withdrawal criterion

1. Section 4.3, Withdrawal Criteria and Procedures for the Patient

Hepatic impairment and Neuroleptic Malignant Syndrome (NMS) are to be added as number "9" and "10" respectively, in the withdrawal criteria list.

(9) Patient has evidence of diminished hepatic function based on the following liver function laboratory tests results:

a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × the upper limit of the normal range (ULN)

b. Alkaline phosphatase (ALP) or total bilirubin >2 × ULN

(10) Patient develops Neuroleptic Malignant Syndrome (NMS)

These changes are **considered substantial** and will be submitted to the UK sites for immediate implementation following an MHRA requirement. These changes will be incorporated into the protocol during the next global amendment. 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]

Name: [redacted]

Title: [redacted]

Department: [redacted], Teva Pharmaceuticals

16.7. Letter of Clarification 05 Dated 16 January 2019

LETTER OF CLARIFICATION 05

Study number: TV50717-CNS-30080

Clinical Study Protocol Amendment 01

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents (RECLAIM-DCP)

Dated 20 December 2018

IND number: 139700; EudraCT number: 2018-003742-17

16 Jan 2019

Dear Investigator:

The purpose of this letter is to clarify and revise the following:

1) Appendix C, Section 5a: it currently reads "Week 16/End of Study follow-up visit (day 112±2 days total from baseline, **or 1 week after ET)**"; **"or 1 week after ET"** needs to be removed, since early termination (ET) patients have a FU visit 2 weeks after ET (equivalent to activities described in the week 17 visit).

2) Pages 12, 47 and 53: it currently reads "All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after **their last dose of IMP**".

   To properly align with the follow up visit described under Section 5.b on page 144 it should read "All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after **ET.**"

3) Page 48, Figure 1: the Week 17 visit is currently labeled the "End-of-Study Visit," whereas the Week 16 visit should be labeled the "End-of-Study Visit."

4) Page 93, Section 8.1: [redacted]

   with a newly added reference to the pharmacogenetics (PGx) informed consent form (ICF) for better overall clarity:

   "patient or parent(s)/legally acceptable representative must provide written informed consent.

pharmacogenetics (PGx) evaluation
- release of patient's study videos for use in publications or educational presentations"

These changes are not considered substantial and 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 contac [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

16.8. Amendment 01 Dated 20 December 2018

The primary reason for this amendment is to address comments and recommendations from the Food and Drug Administration in relation to study design and the scales used to perform assessments. This amendment is considered to be substantial (ie, requires approval by competent authorities, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial 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.

Table 3 (Study Procedures and Assessments) has been revised to reflect changes described below.

Other minor or editorial 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.

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE affected by this change:		
Confidentiality Statement This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D~~.~~ and/or its affiliates.	**Confidentiality Statement** This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D and/or its affiliates.	Confidentiality language updated per template. Letter of Clarification 04
2. STUDY OBJECTIVES AND ENDPOINTS		
2.1 Primary and Secondary Study Objectives and Endpoints "Intext table" (Other sections affected by anyone of these changes: Sections 2.1, 2.1.2, 3.1, 3.4, 3.5, 4.1, 5.2.3, 5.10.3, 6.2.1, 6.3.5, 7, 7.2, 9.2.2, 9.5.1, 9.5.2, 9.5.2.1, 9.5.2.2, 9.5.3, 9.5.4, 9.5.4.1, 9.5.5, 9.6, 9.7, Table 3, and Appendix C)		
The primary efficacy endpoint is the change from baseline to week 15 in the MD-CRS part II total score (movement disorder severity, centrally read) (TEV-50717 versus placebo).	The primary efficacy endpoint is the change from baseline to week 15 in the MD-CRS part II total score (movement disorder severity, centrally read) (TEV-50717 versus placebo).	Updating the verbiage associated with MD-CRS II and how the scale is to be measured for clarity.
The key secondary efficacy endpoints (TEV-50717 versus placebo) are the following: • MD-CRS part I total score (general assessment, centrally read) change from baseline to week 15 Other efficacy measures and endpoints (TEV-50717 versus placebo) include the following: • MD-CRS Global Index (calculated from MD CRS parts I and II total scores) • PEDI-CAT (ADL, parent/caregiver completed, ~~counter~~ content-balanced version) The safety variables include adverse events (and the number of patients who withdraw from the study due to adverse events), vital signs, laboratory tests (hematology, chemistry, and urinalysis), ECG measurements, CBCL, ESRS, ESS, and the children's C-SSRS.	The key secondary efficacy endpoints (TEV-50717 versus placebo) are the following: • MD-CRS part I total score (general assessment, centrally read) change from baseline to week 15 Other efficacy measures and endpoints (TEV-50717 versus placebo) include the following: • MD-CRS Global Index (calculated from MD CRS parts I and II total scores) • PEDI-CAT (ADL, parent/caregiver completed, content-balanced version) The safety variables include adverse events (and the number of patients who withdraw from the study due to adverse events), vital signs, laboratory tests (hematology, chemistry, and urinalysis), ECG measurements, CBCL, ESRS, ESS, and the children's C-SSRS.	Updating the verbiage associated with MD-CRS I and how the scale is to be measured for clarity.

Original text with changes shown	New wording	Reason/Justification for change
2.1.1. Justification of Primary Endpoint		
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 the severity of the movement disorder. ~~The raw score of part II (0 to 28) is normalized in a scale of 0 to 1 as Index II (MD-CRS II). Similar normalization is done for the part I raw score as Index I (0 to 1) and for the sum of the raw scores of parts I and II as the Global Index (0 to 1).~~	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 the severity of the movement disorder.	Changes following FDA request..
3. STUDY DESIGN		
3.1. General Study Design and Study Schematic Diagram (Other sections affected by this change: Appendix C)		
Screening period (up to 31 days): After informed consent (and written assent and/or co-consent for patients 14 years of age and older, as appropriate) is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history~~,~~; physical and neurological examination~~,~~; laboratory testing~~,~~; 12-lead ECG~~,~~; along with MD-CRS part II ~~rating scale~~ (physician rated, with video ~~recorded~~recording, centrally read with video review, centrally read by the Enrollment Adjudication Board [EAB]) to assess severity of dyskinesia; Clinical Global Impression of Severity (CGI-S) to assess global clinical impression of DCP severity, comorbid CP symptoms, and behavioral status~~. The option~~; children's Columbia-Suicide Severity Rating Scale (C-SSRS); assessment of drug-induced parkinsonism according to the Extrapyramidal Symptom Rating Scale (subscales I and II; ESRS); assessment of change in behavior according to the Child Behavior Checklist (for ages 6-18) (CBCL) questionnaire; and assessment of sedation according to the Epworth Sleepiness Scale (for children and adolescents) (ESS) questionnaire of using a telephone with non-recording live video will be made possible,	Screening period (up to 31 days): After informed consent (and written assent and/or co-consent for patients 14 years of age and older, as appropriate) is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history; physical and neurological examination; laboratory testing; 12-lead ECG; along with MD-CRS part II (physician rated, with video recording, centrally read with video review, centrally read by the Enrollment Adjudication Board [EAB]) to assess severity of dyskinesia; Clinical Global Impression of Severity (CGI-S) to assess global clinical impression of DCP severity, comorbid CP symptoms, and behavioral status; children's Columbia-Suicide Severity Rating Scale (C-SSRS); assessment of drug-induced parkinsonism according to the Extrapyramidal Symptom Rating Scale (subscales I and II; ESRS); assessment of change in behavior according to the Child Behavior Checklist (for ages 6-18) (CBCL) questionnaire; and assessment of sedation according to the Epworth Sleepiness Scale (for children and adolescents) (ESS) questionnaire of using a telephone with non-recording live video will be made possible, and the adoption of live video to support	Clarification has been provided for assessments to be completed during the screening period, and new assessments have been included.

Original text with changes shown	New wording	Reason/Justification for change
and the adoption of live video to support patient/caregiver interview will then be maintained throughout the study for the evaluation of safety/tolerability and dyskinesia severity. Screening may be conducted over 2 separate visits at the discretion of the investigator. The diagnosis of CP and DCP will be established based on clinical features as described in the inclusion/exclusion criteria. The EAB will also confirm, based on video recordings, that choreiform is clinically the predominant movement disorder of the patient's DCP. EAB assessment results will be available to the investigator prior to baseline and randomization. At all other visits, the MD-CRS part II ~~rating scale~~ will be administered by the investigational center physician and video ~~recorded~~ review for central-blinded reading.	patient/caregiver interview will then be maintained throughout the study for the evaluation of safety/tolerability and dyskinesia severity. Screening may be conducted over 2 separate visits at the discretion of the investigator. The diagnosis of CP and DCP will be established based on clinical features as described in the inclusion/exclusion criteria. The EAB will also confirm, based on video recordings, that choreiform is clinically the predominant movement disorder of the patient's DCP. EAB assessment results will be available to the investigator prior to baseline and randomization. At all other visits, the MD-CRS part II will be administered by the investigational center physician and video review for central blinded reading.	
Titration period (7 weeks): Patients who remain eligible for participation in the study will be randomized at the baseline visit (day 1) and instructed to take the first dose of blinded IMP the following morning, ~~without regard to food.~~ with food (eg, a snack) and should not be taken on an empty stomach. Safety/tolerability in-clinic evaluations during titration include assessment of vital signs, monitoring for adverse events and concomitant medications, 12-lead ECGs, ~~and rating scales for depression and suicidality.~~identifying subjects at risk for suicide according to the C-SSRS questionnaire, 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.	Titration period (7 weeks): Patients who remain eligible for participation in the study will be randomized at the baseline visit (day 1) and instructed to take the first dose of blinded IMP the following morning, with food (eg, a snack) and should not be taken on an empty stomach. Safety/tolerability in-clinic evaluations during titration include assessment of vital signs, monitoring for adverse events and concomitant medications, 12-lead ECGs, identifying subjects at risk for suicide according to the C-SSRS questionnaire, 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.	Clarification has been provided that the IMP should be administered with food. Assessments to be completed during the titration period have been updated and added.
3.5. Schedule of Study Procedures and Assessments (Other sections affected by any one of these changes: Section 6.1, 6.2.1, 6.2.2, 6.2.3, 6.3.7, 6.3.8, Appendix C, and Appendix I)		
Row: Study week *Column: Follow-up* 16/EOS (Day 112)	*Row: Study week* *Column: Follow-up* 16/EOS (Day 112)	The Schedule of Assessments has been updated to reflect all changes made to the study design. Assessments and time points

Original text with changes shown	New wording	Reason/Justification for change
Row: Vital signs and weight *Column: Screening, -31 days* X	*Row: Vital signs and weight* *Column: Screening, -31 days* X	for assessments have been added and/or removed as indicated (left). Three new safety scales have been included. Footnotes have also been updated for clarity and to align with updates made to the study design.
Row: Physical examination *Column: BL, Day 1* X	*Row: Physical examination* *Column: BL, Day 1* X	
Row: Neurological examination *Column: BL, Day 1* X	*Row: Neurological examination* *Column: BL, Day 1* X	
Row: Urine drug screen *Column: Titration, Week 3 (Day 21)* X	*Row: Urine drug screen* *Column: Titration, Week 3 (Day 21)* X	
Row: Urine drug screen *Column: Maintenance, Week 9 (Day 63)* X	*Row: Urine drug screen* *Column: Maintenance, Week 9 (Day 63)* X	
Row: Urine drug screen *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: Urine drug screen* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: β-HCG test *Column: Titration, Week 3 (Day 21)* X	*Row: β-HCG test* *Column: Titration, Week 3 (Day 21)* X	
Row: β-HCG test *Column: Titration, Week 7 (Day 49)* X	*Row: β-HCG test* *Column: Titration, Week 7 (Day 49)* X	
Row: β-HCG test *Column: Maintenance, Week 9 (Day 63)* X	*Row: β-HCG test* *Column: Maintenance, Week 9 (Day 63)* X	
Row: β-HCG test	*Row: β-HCG test*	

Original text with changes shown	New wording	Reason/Justification for change
Column: Maintenance, Week 12 (Day 84) X	*Column: Maintenance, Week 12 (Day 84)* X	
Row: β-HCG test *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: β-HCG test* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: MD-CRS part I (physician rated, with video recording) *Column: Study week*	*MD-CRS part I (physician rated, with video recording)*	
Row: MD-CRS part I (physician rated, with video recording) *Column: Screening, -31 days* ~~X~~	*Row: MD-CRS part I (physician rated, with video recording)* *Column: Screening, -31 days*	
Row: MD-CRS part I (physician rated, with video recording) *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: MD-CRS part I (physician rated, with video recording)* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: MD-CRS part I (centrally read, with video review) *Column: Study week*	*Row: MD-CRS part I (centrally read, with video review)* *Column: Study week*	
Row: MD-CRS part I (centrally read, with video review) *Column: BL, Day 1* X	*Row: MD-CRS part I (centrally read, with video review)* *Column: BL, Day 1* X	
Row: MD-CRS part I (centrally read, with video review) *Column: Maintenance, Week 9 (Day 63)* X	*Row: MD-CRS part I (centrally read, with video review)* *Column: Maintenance, Week 9 (Day 63)* X	
Row: MD-CRS part I (centrally read, with video review) *Column: Maintenance, Week 12 (Day 84)* X	*Row: MD-CRS part I (centrally read, with video review)* *Column: Maintenance, Week 12 (Day 84)* X	
Row: MD-CRS part I (centrally read, with video review) *Column: Maintenance, Week 15/ET (Day 105)*	*Row: MD-CRS part I (centrally read, with video review)* *Column: Maintenance, Week 15/ET (Day 105)*	

Original text with changes shown	New wording	Reason/Justification for change
X	X	
Row: MD-CRS part I (centrally read, with video review) *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: MD-CRS part I (centrally read, with video review)* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: MD-CRS part II (physician rated, with video recording) *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: MD-CRS part II (physician rated, with video recording)* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: MD-CRS part II (centrally read, with video ~~recording~~review) *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: MD-CRS part II (centrally read, with video review)* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: CaGI-I *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: CaGI-I* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: CGI-I (global, physician rated) *Column: Follow-up Week 16/EOS (Day 112)* X	*Row: CGI-I (global, physician rated)* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: CGI-S (global, physician rated) *Column: Screening, -31 days* X	*Row: CGI-S (global, physician rated)* *Column: Screening, -31 days* X	
Row: CGI-S (global, physician rated) *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: CGI-S (global, physician rated)* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: PGI-I (global, patient/caregiver) *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: PGI-I (global, patient/caregiver)* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: ESRS subscales I and II *Column: Study week*	*Row: ESRS subscales I and II* *Column: Study week*	

Original text with changes shown	New wording	Reason/Justification for change
Row: ESRS subscales I and II *Column: Screening, -31 days* X	*Row: ESRS subscales I and II* *Column: Screening, -31 days* X	
Row: ESRS subscales I and II *Column: BL, Day 1* X	*Row: ESRS subscales I and II* *Column: BL, Day 1* X	
Row: ESRS subscales I and II *Column: Titration, Week 3 (Day 21)* X	*Row: ESRS subscales I and II* *Column: Titration, Week 3 (Day 21)* X	
Row: ESRS subscales I and II *Column: Titration, Week 7 (Day 49)* X	*Row: ESRS subscales I and II* *Column: Titration, Week 7 (Day 49)* X	
Row: ESRS subscales I and II *Column: Maintenance, Week 9 (Day 63)* X	*Row: ESRS subscales I and II* *Column: Maintenance, Week 9 (Day 63)* X	
Row: ESRS subscales I and II *Column: Maintenance, Week 12 (Day 84)* X	*Row: ESRS subscales I and II* *Column: Maintenance, Week 12 (Day 84)* X	
Row: ESRS subscales I and II *Column: Maintenance, Week 15/ET (Day 105)* X	*Row: ESRS subscales I and II* *Column: Maintenance, Week 15/ET (Day 105)* X	
Row: ESRS subscales I and II *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: ESRS subscales I and II* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: ESRS subscales I and II *Column: Unscheduled* X	*Row: ESRS subscales I and II* *Column: Unscheduled* X	
Row: CBCL	*Row: CBCL*	

Original text with changes shown	New wording	Reason/Justification for change
Column: Study week	*Column: Study week*	
Row CBCL *Column: Screening, -31 days* X	*Row: CBCL* *Column: Screening, -31 days* X	
Row: CBCL *Column: BL, Day 1* X	*Row: CBCL* *Column: BL, Day 1* X	
Row: CBCL *Column: Titration, Week 3 (Day 21)* X	*Row: CBCL* *Column: Titration, Week 3 (Day 21)* X	
Row: ESRS subscales I and II *Column: Titration, Week 7 (Day 49)* X	*Row: ESRS subscales I and II* *Column: Titration, Week 7 (Day 49)* X	
Row: CBCL *Column: Maintenance, Week 9 (Day 63)* X	*Row: CBCL* *Column: Maintenance, Week 9 (Day 63)* X	
Row: CBCL *Column: Maintenance, Week 12 (Day 84)* X	*Row: CBCL* *Column: Maintenance, Week 12 (Day 84)* X	
Row: CBCL *Column: Maintenance, Week 15/ET (Day 105)* X	*Row: CBCL* *Column: Maintenance, Week 15/ET (Day 105)* X	
Row: CBCL *Column: Follow-up, Week 16/EOS (Day 112)* X	*Row: CBCL* *Column: Follow-up, Week 16/EOS (Day 112)* X	
Row: CBCL *Column: Unscheduled* X	*Row: CBCL* *Column: Unscheduled* X	

Original text with changes shown	New wording	Reason/Justification for change
Row: Assess adverse events *Column: Screening, -31 days* ~~X~~	*Row: Assess adverse events* *Column: Screening, -31 days*	
4.2 Patient Exclusion Criteria		
Not applicable.	12. Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, other cardiac arrhythmias, or uncompensated heart failure.	Included an additional exclusion criteria pertaining to cardiac history. Letter of Clarification 03
~~13~~14. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5 × ULN at screening.	14. Patient has evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5 × ULN at screening.	Added the serum creatinine range that will indicate clinically significant renal impairment for clarity. Letter of Clarification 03
5.1. Investigational Medicinal Products Used in the Study		
5.1.1. Test Investigational Medicinal Product (Other sections affected by this change: Section 3.1, 5.1.1.1, and 5.1.1.2)		
Test IMP (TEV-50717 [deutetrabenazine, previously SD-809]) will be administered as oral tablets~~. The IMP is a matrix formulation and is designed to be taken without regard to food. The effects of food on the bioavailability of TEV-50717 were studied in patients administered a single dose with and without food. Food had no effect on the area under the plasma drug concentration-time curve of α-HTBZ or β-HTBZ, although the maximum serum concentration was increased by approximately 50% in the presence of food (AUSTEDO USPI 2017).~~ with food (eg, a snack) and should not be taken on an empty stomach.	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.	Updated guidance of administration of IMP.
5.8. Temporary Discontinuation of Investigational Medicinal Product		
Dose adjustments should be made based on all available information, including the patient's and parent's/caregiver's reports of adverse events and motor function improvement, the clinical assessment of safety and efficacy by the investigator, and information from rating scales. **If more than 1 dose reduction is required for an adverse event, the medical monitor**	Dose adjustments should be made based on all available information, including the patient's and parent's/caregiver's reports of adverse events and motor function improvement, the clinical assessment of safety and efficacy by the investigator, and information from rating scales. **If more than 1 dose reduction is required for an adverse event, the medical monitor**	Updated guidance on dose adjustments for temporary discontinuation of IMP based on the number of dose reductions or duration of dose suspension. Letter of Clarification 04

Original text with changes shown	New wording	Reason/Justification for change
should be notified. Suspension of IMP treatment for up to 1 week, if warranted, is allowed. If the patient restarts IMP within 7 days of suspension, the full dose of IMP may be resumed without titration at the same dose level or 1 dose lower (last tolerated dose). Suspension of IMP treatment for adverse events must be reviewed with the medical monitor before IMP 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 reduction or suspension is allowed once during the titration period and once during the maintenance period. Patients who restart IMP treatment will remain at the current dose throughout that period with no further dose changes 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. If a dose suspension occurs before a scheduled clinic visit, an unscheduled visit should be scheduled as soon as possible so that efficacy evaluations can be performed at least 5 days after the change. 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. If a patient's serum potassium or magnesium level falls below the lower limit of normal, IMP must be suspended. The medical monitor must be contacted to determine the appropriate investigation and treatment. IMP treatment may only be restarted once serum potassium and/or magnesium levels have normalized. The patients who restart IMP treatment will follow the	**should be notified.** Suspension of IMP treatment for up to 1 week, if warranted, is allowed. If the patient restarts IMP within 7 days of suspension, the full dose of IMP may be resumed without titration at the same dose level or 1 dose lower (last tolerated dose). Suspension of IMP treatment for adverse events must be reviewed with the medical monitor before IMP 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 reduction or suspension is allowed once during the titration period and once during the maintenance period. Patients who restart IMP treatment will remain at the current dose throughout that period with no further dose changes 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. If a dose suspension occurs before a scheduled clinic visit, an unscheduled visit should be scheduled as soon as possible so that efficacy evaluations can be performed at least 5 days after the change. 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. If a patient's serum potassium or magnesium level falls below the lower limit of normal, IMP must be suspended. The medical monitor must be contacted to determine the appropriate investigation and treatment. IMP treatment may only be restarted once serum potassium and/or magnesium levels have normalized. The patients who restart IMP treatment will follow the	

Original text with changes shown	New wording	Reason/Justification for change
visit schedule as outlined in Table 3. Patients who withdraw from the study will proceed as described in Section 4.3.	visit schedule as outlined in Table 3. Patients who withdraw from the study will proceed as described in Section 4.3.	
5.11. Total Blood Volume (Other sections affected by this change: Appendix I)		
The total blood volume to be collected for each patient in this study is approximately ~~41~~40 mL (at maximum), as detailed in Appendix I.	The total blood volume to be collected for each patient in this study is approximately 40 mL (at maximum), as detailed in Appendix I.	Updated total blood draw volumes to align with updated volumes presented in table 12.
6.1. Primary Efficacy Measure		
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). ~~For data analysis, the raw score of MD-CRS part II items (0 to 28) is normalized to a 0 to 1 range as Index II (MD-CRS II). Raw scores (0 to 28) reflecting severity of the movement disorder will be used to qualify a patient for inclusion in the study.~~	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).	Streamlined the description of the MD-CRS part II to include only necessary protocol details. Further details to be provided in the SAP.
6.2. Key Secondary Efficacy Measures		
6.2.1. Movement Disorder-Childhood Rating Scale Part I Total Score		
The MD-CRS part I evaluates 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 ~~raw~~minimum score ~~of MD-CRS part I (~~is 0 ~~to~~and the maximum score is 60~~) is normalized to a 0 to 1 range as Index I (MD-CRS I)~~.	The MD-CRS part I evaluates 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 of MD-CRS part I is 0 and the maximum score is 60).	Streamlined the description of the MD-CRS part I to include only necessary protocol details. Further details to be provided in the SAP.
6.3. Other Efficacy Measures		
6.3.1. Movement Disorder-Childhood Rating Scale Global Index		

Original text with changes shown	New wording	Reason/Justification for change
The MD-CRS Global Index is a global measure of the MD-CRS that consolidates the information from ~~Indexes~~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 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.	Streamlined the description of the calculation of the MD-CRS Global Index.
6.3.4. Unified Huntington's Disease Rating Scale-Total Maximal Dystonia		
The UHDRS-Total Maximal Dystonia (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-Total Maximal Dystonia (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).	Streamlined the description of the method to measure the UHDRS-TMD.
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).	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).	Updated language based on communications with regulatory authorities and their feedback.
7.2.2. Child Behavior Checklist (for Ages 6-18) (Other sections affected by this change: Section 3.5, Table 3)		
Not applicable.	The CBCL assesses behavioral and emotional status in children ages 6 through 18 years of age as reported by the parent/caregiver (Achenbach and Ruffle 2000; Achenbach 2005). The full CBCL has two 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	Added section to include a description of an additional safety scale to be assessed in the study (ie, CBCL).

Original text with changes shown	New wording	Reason/Justification for change
	within the last 6 months". For each item, the parent/caregiver will circle 0 if the item is not true of their child, 1 if the item is somewhat or sometimes true, and 2 if the item is very true or often true. The 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. 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 and Syndrome Scales) will be completed at screening and at week 15/ET. Only the CBCL Syndrome scale will be completed at baseline, weeks 3, 7, 9, 12, and 16/EOS.	
7.2.3. Extrapyramidal Symptom Rating Scale		
Not applicable.	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 screening; baseline; and weeks 3, 7, 9, 12, 15/ET, and 16/EOS. The 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	Added section to include a description of an additional safety scale to be assessed in the study (ie, ESRS).

Original text with changes shown	New wording	Reason/Justification for change
	account the verbal report of the patient on: 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. The subscale II of the ESRS questionnaire for evaluation of parkinsonism and akathisia includes 17 items with scores ranging from 0-102 to assess the following: tremor (0–48), gait and posture (0–6), postural stability (0 6), rigidity (0–24), expressive automatic movements (0–6), bradykinesia (0-6), and akathisia (0–6).	
7.2.4. Epworth Sleepiness Scale (for Children and Adolescents)		
Not applicable.	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. In 2017, Janssen et al 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 screening; baseline; and weeks 3, 7, 9, 12, 15/ET, and 16/EOS. The ESS asks respondents to rate, on a 4 point Likert scale (0–3), their usual chances of dozing off or falling asleep in different situations or activities that most people engage in as part of their daily lives. The total ESS score is the sum of 8 item scores and can range between 0 and 24 with 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	Added section to include a description of an additional safety scale to be assessed in the study (ie, ESS).

Original text with changes shown	New wording	Reason/Justification for change
	• 0=would never fall asleep • 1=slight chance of falling asleep • 2=moderate chance of falling asleep • 3=high chance of falling asleep	
7.11. Neurological Examinations		
Any neurological examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with the ~~screening~~baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.	Any neurological examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with the baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.	Updated to clarify that the baseline value will be used as a comparator for neurological examination findings.
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. Of note, any formulation/derivative of cannabis is prohibited during the study.	Updated language to include a statement on the prohibition of cannabis during the study.
8.3.1. CYP2D6 Genotyping/Pharmacogenetics (Other sections affected by this change: Appendix I)		
At the screening visit, a mandatory blood sample (~~4~~3.0 to 5.0 mL) will be obtained for analysis of CYP2D6 genotype from all patients in the study at the time point detailed in Table 3. The CYP2D6 genotype results will be provided to the RTSM, which drives each patient's dose regimen, and the patient's genotype for CYP2D6 will remain blinded during the conduct of the study. [redacted]	At the screening visit, a mandatory blood sample (3.0 to 5.0 mL) will be obtained for analysis of CYP2D6 genotype from all patients in the study at the time point detailed in Table 3. The CYP2D6 genotype results will be provided to the RTSM, which drives each patient's dose regimen, and the patient's genotype for CYP2D6 will remain blinded during the conduct of the study. [redacted]	Updated to correct the blood volume to be taken at screening. [redacted]

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
9.1. Sample Size and Power Considerations		
The initial sample size estimation of approximately 185 patients randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 124 in the TEV-50717 group; approximately 61 in the placebo group) is the sample size required to obtain a statistically significant result in the primary analysis based on a 1-sided test for mean difference at a significance level of α=0.025 with a power of approximately 90%, assuming a mean difference of ~~0.063~~1.8 and a standard deviation (SD) of ~~0.126~~3.5 in each treatment group. The initial assumptions regarding the mean difference and SD are based on the change from baseline to month 6 in patients treated with trihexyphenidyl reported by Battini et al (2014), assuming an effect size of 55% for TEV-50717 versus placebo. The effect size of 55% was assumed based on the observed effect sizes of TEV-50717 in the pivotal studies in HD and TD. In the current study, these assumptions correspond to a mean difference of 2.0~~.07~~ in MD-CRS part II total score and an SD of ~~0.126~~3.5 in each treatment group. The rate of missing not at random (MNAR) data for the primary analysis is expected to be 10%. MNAR data will be imputed in a conservative manner as if they were obtained from patients in the placebo treatment group,	The initial sample size estimation of approximately 185 patients randomized to TEV-50717 versus placebo in a 2:1 ratio (approximately 124 in the TEV-50717 group; approximately 61 in the placebo group) is the sample size required to obtain a statistically significant result in the primary analysis based on a 1-sided test for mean difference at a significance level of α=0.025 with a power of approximately 90%, assuming a mean difference of 1.8 and a standard deviation (SD) of 3.5 in each treatment group. The initial assumptions regarding the mean difference and SD are based on the change from baseline to month 6 in patients treated with trihexyphenidyl reported by Battini et al (2014), assuming an effect size of 55% for TEV-50717 versus placebo. The effect size of 55% was assumed based on the observed effect sizes of TEV-50717 in the pivotal studies in HD and TD. In the current study, these assumptions correspond to a mean difference of 2.0 in MD-CRS part II total score and an SD of 3.5 in each treatment group. The rate of missing not at random (MNAR) data for the primary analysis is expected to be 10%. MNAR data will be imputed in a conservative manner as if they were obtained from patients in the placebo treatment	Updated the mean difference and SD values used for this study to more accurately represent sample size and power considerations.

Original text with changes shown	New wording	Reason/Justification for change
regardless of the actual treatment group. As a result, the mean difference is expected to be reduced from 2.0~~.07~~ to ~~0.063~~1.8 in the primary analysis. The impact of the missing data imputation on the SD is negligible.	group, regardless of the actual treatment group. As a result, the mean difference is expected to be reduced from 2.0 to 1.8 in the primary analysis. The impact of the missing data imputation on the SD is negligible.	
9.2.2. Modified Intent to Treat Analysis Set		
The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including all randomized patients with ~~centrally read total raw scores of ≥10 on MD-CRS part II items at baseline, and~~ at least 1 post-baseline centrally read MD-CRS part II assessment.	The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including all randomized patients with at least 1 post-baseline centrally read MD-CRS part II assessment.	The mITT analysis set was clarified to state that all randomized patients who had at least 1 post-baseline centrally read MD-CRS part II assessment were included.
9.2.4. Per-Protocol Analysis Set		
The per-protocol (PP) analysis set is a subset of the mITT analysis set including only patients who meet the following criteria: • compliant with study medication (80% to 105%) • complete the study without any major protocol deviations that may impact efficacy • centrally read baseline MD-CRS part II total score of ≥10	The per-protocol (PP) analysis set is a subset of the mITT analysis set including only patients who meet the following criteria: • compliant with study medication (80% to 105%) • complete the study without any major protocol deviations that may impact efficacy • centrally read baseline MD-CRS part II total score of ≥10	An additional criteria based on the MD-CRS part II total score was included for the PP analysis set.
9.5.4.1. Secondary Efficacy Analysis		
Not applicable.	In addition, sensitivity analyses for the key secondary endpoints will be performed in the same fashion as the primary endpoint.	Updated to clarify sensitivity analysis of key secondary endpoints.
9.8. Safety Endpoints and Analysis		
Not applicable.	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.	Updated the safety analysis to include the 3 new safety scales that will be assessed during the study.
APPENDIX H. LIST OF ALLOWED AND PROHIBITED MEDICATIONS		
Benzodiazepines, muscle relaxants, (including tizanidine), trihexyphenidyl, baclofen (oral and	Benzodiazepines, muscle relaxants, (including tizanidine), trihexyphenidyl, baclofen (oral and	Letter of Clarification 01 Updated the list of allowed medications to

Original text with changes shown	New wording	Reason/Justification for change
intrathecal), gabapentin, and levetiracetam	intrathecal), gabapentin, and levetiracetam	include tizanidine.
APPENDIX I. TOTAL BLOOD VOLUME		
Table 12 from the original amendment has been reconstructed.	Table 12 was revised to reflect the following changes: 1. Maximum blood draw was revised to a maximum of 40 mL (from 41 mL) 2. Blood volume per test per visit and the total for each visit was added. 3. β-HCG and prothrombin/INR were added. Blood draws at week 16/EOS and unscheduled visits were clarified as obtained at the investigator's discretion.	Letter of Clarification 04 Blood draw volumes were updated, so table 12 was updated to align with blood draws dictated throughout the protocol.
Global		
Updated amendment number, dates, section numbers, and tables of contents. Corrected typos; errors in punctuation, grammar, and formatting; and inconsistencies in style.	Not applicable.	Clarification

16.9. Letter of Clarification 04 Dated 05 December 2018

LETTER OF CLARIFICATION 04

Study number: TV50717-CNS-30080

Clinical Study Protocol

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents (RECLAIM-DCP)

Dated 27 September 2018

IND number: 139700; EudraCT number: 2018-003742-17

05 Dec 2018

Dear Investigator:

The purpose of this letter of clarification is to describe:

- Management of low serum potassium or magnesium
- Management of treatment suspension
- Clarification on blood volumes taken during the study
- Correction of MD-CRS II body part listing on page 70 of the protocol
- Clarification regarding Teva affiliates

1) Management of low serum potassium or magnesium

If a patient's serum potassium or magnesium falls below the lower limit of normal, IMP must be suspended. The medical monitor must be contacted to determine the appropriate investigation and treatment. IMP may only be restarted once serum potassium or magnesium has normalized.

2) Management of treatment suspension (Clarification to Section 5.1.1.2 Dose Modification and Dose Stratification)

Suspension of study medication for up to 1 week, if warranted, is allowed. If the patient restarts study medication within 7 days of suspension, the full dose of IMP may be resumed at the same dose level or 1 dose level less (ie, the last tolerated dose) at the investigators prerogative.

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 AE form.

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If a dose reduction or suspension 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.

Dose reduction or suspension is allowed once during the titration period and once during the maintenance period. Patients who restart IMP treatment will remain at the current dose throughout that period with no further dose changes, and will otherwise follow the visit schedule as outlined in the protocol.

3) Clarification on blood volumes taken during study

Blood draw volumes were updated and differ from those currently in the protocol (table 12) with 1 visit having a slightly higher blood draw: Week 15 has a max. blood draw of 21.5 mL instead of the 19 mL indicated in the protocol.

Updated table depicting the blood draw volumes in mL:

Test	SCR	Week 15	Week 16	UNC
Pharmacokinetics		8		
Chemistry	3.5 / 1.25	3.5 / 1.25	[3.5 / 1.25]	[3.5 / 1.25]
Hematology	2.0 / 1.0	2.0 / 1.0	[2.0 / 1.0]	[2.0 / 1.0]
CYP2D6	5.0 / 3.0			
HCG	3.5 / 1.25	3.5 / 1.25		[3.5]
Prothrombin/INR	4.5	4.5	[4.5]	[4.5]
Total Volume per patient per visit (mL)	18.5	21.5	[10]	

Abbreviations: CYP2D6= cytochrome P450 2D6; HCG= human chorionic gonadotropin; INR= international normalized ratio; SCR=screening visit; UNC=unscheduled visit
Notes: Red values indicate minimal blood volumes. Values in square brackets indicate possible blood draws.

4) Correction of MD-CRS II body part listing on page 70 of the protocol

The MD-CRS II body part listing currently reads: "*The 7 body regions are (i) eye and periorbital region, (ii) face, (iii) tongue and **periorbital** region, (iv) neck, (v) trunk, (vi) upper limb, and (vii) lower limb.*"

It should read: "*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.*"

5) Clarification regarding Teva affiliates

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TEVA Pharmaceuticals

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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16.10. Letter of Clarification 03 Dated 22 November 2018

LETTER OF CLARIFICATION 03

Study number: TV50717-CNS-30080

Clinical Study Protocol

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents (RECLAIM-DCP)

Dated 27 September 2018

IND number: 139700; EudraCT number: 2018-003742-17

22 Nov 2018

Dear Investigator:

The purpose of this letter of clarification is to describe:

- Exclusion criterion 13
- Addition of an exclusion criterion
- Correction of PEDI-CAT version

1) To clarify exclusion criterion 13:

Exclusion criterion 13 currently reads "*Patient has evidence of clinically significant renal impairment*". To clarify the definition of clinically significant renal impairment, it should read "*Patient has evidence of clinically significant renal impairment,* ***indicated by a serum creatinine >1.5 × ULN at screening***".

2) Addition of an additional exclusion criterion:

The following exclusion criterion will be added as exclusion criterion 19: "*Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, other cardiac arrhythmias, or uncompensated heart failure*".

3) Correction of PEDI-CAT version:

When describing the PEDI-CAT version, the protocol currently reads "*counter-balanced*". It should read "***content****-balanced*".

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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

16.11. Letter of Clarification 02 Dated 16 November 2018

LETTER OF CLARIFICATION 02

Study number: TV50717-CNS-30080

Clinical Study Protocol

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents (RECLAIM-DCP)

Dated 27 September 2018

IND number: 139700; EudraCT number: 2018-003742-17

16 Nov 2018

Dear Investigator:

The purpose of this letter of clarification is to describe:

- Management of low serum potassium or magnesium
- Management of treatment suspension
- Clarification on blood volumes taken during the study
- Correction of MD-CRS II body part listing on page 70 of the protocol
- Clarification regarding Teva affiliates

1) Management of low serum potassium or magnesium

If a patient's serum potassium or magnesium falls below the lower limit of normal, IMP must be suspended. The medical monitor must be contacted to determine the appropriate investigation and treatment. IMP may only be restarted once serum potassium or magnesium has normalized.

2) Management of treatment suspension

Suspension of study medication for up to 1 week, if warranted, is allowed. If the patient restarts study medication within 7 days of suspension, the full dose of IMP may be resumed at the same dose level or 1 dose level less (ie, the last tolerated dose) at the investigators prerogative.

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 AE form.

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If a dose reduction or suspension 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.

Dose reduction or suspension is allowed once during the titration period and once during the maintenance period. Patients who restart IMP treatment will remain at the current dose throughout that period with no further dose changes, and will otherwise follow the visit schedule as outlined in the protocol.

3) Clarification on blood volumes taken during study

Blood draw volumes were updated and differ from those currently in the protocol (table 12) with 1 visit having a slightly higher blood draw: Week 15 has a max. blood draw of 21.5 mL instead of the 19 mL indicated in the protocol.

Updated table depicting the blood draw volumes in mL:

Test	SCR	Week 15	Week 16	UNC
Pharmacokinetics		8		
Chemistry	3.5 / 1.25	3.5 / 1.25	[3.5 / 1.25]	[3.5 / 1.25]
Hematology	2.0 / 1.0	2.0 / 1.0	[2.0 / 1.0]	[2.0 / 1.0]
CYP2D6	5.0 / 3.0			
HCG	3.5 / 1.25	3.5 / 1.25		[3.5]
Prothrombin/INR	4.5	4.5	[4.5]	[4.5]
Total Volume per patient per visit (mL)	18.5	21.5	[10]	

Abbreviations: CYP2D6= cytochrome P450 2D6; HCG= human chorionic gonadotropin; INR= international normalized ratio; SCR=screening visit; UNC=unscheduled visit
Notes: Red values indicate minimal blood volumes. Values in square brackets indicate possible blood draws.

4) Correction of MD-CRS II body part listing on page 70 of the protocol

The MD-CRS II body part listing currently reads: "*The 7 body regions are (i) eye and periorbital region, (ii) face, (iii) tongue and* ***periorbital*** *region, (iv) neck, (v) trunk, (vi) upper limb, and (vii) lower limb.*"

It should read: "*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.*"

5) Clarification regarding Teva affiliates

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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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16.12. Letter of Clarification 01 Dated 17 October 2018

LETTER OF CLARIFICATION 01

Study number: TV50717-CNS-30080

Clinical Study Protocol

A Randomized, Double-Blind, Placebo-Controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Dyskinesia in Cerebral Palsy in Children and Adolescents (RECLAIM-DCP)

Dated 27 September 2018

IND number: 139700; EudraCT number: 2018-003742-17

17 Oct 2018

Dear Investigator:

The purpose of this letter of clarification is to describe:

- the volume of blood samples taken at screening and the additional patient informed consent related to this sample, and
- tizanidine as an additional allowed medication that is part of the standard of care of cerebral palsy in certain countries.

Screening blood samples

Table 12 in Appendix I of the protocol correctly indicates that 6 ml of blood will be drawn for CYP2D6 genotyping. However, Section 8.3.1 (CYP2D6 Genotyping/Pharmacogenetics) erroneously indicates only 4 ml. The 6 ml volume is the correct volume, allowing for sufficient blood sample for genotyping and for a reserve aliquot in case the first analysis is not successfully completed.

The second paragraph in Section 8.3.1 explains that the remaining (left-over) blood sample may be used for future optional genetic analysis (pharmacogenetics testing), providing that the patient is willing and has provided his/her consent in a separate informed consent form for this purpose. To clarify, the blood sample for CYP2D6 genotyping is mandatory, and only the consent for the use of remaining blood sample for possible pharmacogenetics testing is optional and requires a separate informed consent.

Allowed/prohibited medication

The use of tizanidine, a muscle relaxant, is allowed in this study, if tizanidine's primary use is not for dyskinesia, and if the dosing of tizanidine has been stable for at least 4 weeks before screening.

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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

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] Teva Branded Pharmaceutical Products R&D, Inc Cell [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]
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study	[redacted] Teva Pharmaceutical Industries, [redacted] Cell: [redacted]
Study Principal Investigator	[redacted] Vanderbilt University Medical Center, Department of Neurology 1161 21st Avenue South A-0118 MCN Nashville, TN 37232-2551 Tel: [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] Tel: [redacted] Cell [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]
Pharmacokinetic Samples	Watson Pharma Pvt. Ltd. Seawoods Grand Central, Tower 2 Level-11, Wing-E, Plot No. R-1 Sector 40, Nerul, Navi Mumbai 400706 Tel: [redacted] Contact: [redacted] [redacted] Bioanalytical Operations [redacted]
Central Electrocardiogram Evaluation	Spaulding Medical, LLC 525 S. Silverbrook Drive West Bend, WI 53095 Tel: [redacted]
Randomization and Trial Supply Management (RTSM) vendor	Calyx 4 Canal Street Nottingham, United Kingdom, NG1 7EH Tel: [redacted]
Scales and Central Rater for MD-CRS	Signant Health 785 Arbor Way Blue Bell, PA 19422 Tel: [redacted]

APPENDIX B. INDEPENDENT DATA MONITORING COMMITTEE

When approximately 50 patients have completed the study (including follow-up), an independent Data Monitoring Committee (iDMC) will perform an unblinded non-binding interim analysis (IA) for futility based on centrally read Movement Disorder-Childhood Rating Scale part II (MD-CRS part II) total score. Based on the results of the IA, the study may be stopped.

The iDMC sessions can be open or closed. During open sessions, representatives of the sponsor and the Steering Committee may be present, and information is provided and discussed in a blinded fashion. During closed sessions, the only participants are members of the iDMC and the designated unblinded statistician (if approved to be present).

Details on how the iDMC chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study can be seen in the iDMC charter. The sponsor will work closely with the committee to provide the necessary data for review.

The conduct and specific details regarding the iDMC sessions and requests to unblind any investigational medicinal product assignments are outlined in the iDMC charter.

Further details are given in the Data Monitoring Plan and iDMC Statistical Analysis Plan.

APPENDIX C. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. **Procedures for Screening (Day -31)**

The screening visit will take place not more than 31 days before the baseline visit. Screening may be conducted over 2 separate visits at the discretion of the investigator. The following procedures/assessments will be performed at the screening visit:

- patients, parent(s)/legally accepted representative(s), and caregivers must provide their respective written informed consent and/or assent (as appropriate) before any study-related procedures are performed. Assent/consent may also be provided to 2 optional ICFs:
  - [redacted]
  - use of patient's study videos for future analysis of gait digital markers and release of patient's study videos for use in publications or educational presentations
- review of eligibility criteria
- medical and psychiatric history
- demographics
- vital signs measurements (including orthostatic blood pressure) and weight
- physical examination
- neurological examination
- height
- 12-lead electrocardiogram (ECG)
- clinical laboratory tests (chemistry, hematology, and urinalysis); these tests may be repeated to determine patient eligibility
- urine drug screen; these tests may be repeated to determine patient eligibility
- cytochrome P450 2D6 (CYP2D6) genotype
- beta-human chorionic gonadotropin (β-HCG) serum pregnancy test (for females aged 12 years or older of childbearing potential)
- MD-CRS part II video recording and investigator assessment
- Clinical Global Impression of Severity (CGI-S) (global, physician rated)
- Children's Columbia-Suicide Severity Rating Scale (C-SSRS) (Baseline/Screening)
- Child Behavior Checklist (for ages 6-18) (CBCL), full version (Competence and Syndrome)
- Extrapyramidal Symptom Rating Scale (subscales I and II; ESRS)
- Epworth Sleepiness Scale (for children and adolescents) (ESS)

- concomitant medications
- contact RTSM

2. **Procedures Before Administration of Investigational Medicinal Product (Baseline [Day 1±0 days])**

Patients who meet the inclusion and exclusion criteria at the screening visit will continue to the baseline visit when baseline assessments will be conducted. The investigator should review all available data to determine patient eligibility before randomizing to the study.

The following procedures/assessments will be performed at the baseline visit:

- review of eligibility criteria
- assignment of randomization/treatment numbers after patient eligibility is confirmed based on all available visit assessments, and entry into case report form (CRF)
- vital signs measurements (including orthostatic blood pressure) and weight
- physical examination
- neurological examination
- urine pregnancy test
- MD-CRS part I video recording and investigator assessment
- MD-CRS part II video recording and investigator assessment
- Clinical Global Impression of Severity (CGI-S) (global, physician rated)
- Pediatric Evaluation Disability Inventory-Computer Adapted Test (PEDI-CAT) (activities of daily living [ADL], caregiver completed, content-balanced version)
- Cerebral Palsy module of Pediatric Quality of Life Inventory (PedsQL) (quality of life [QoL], patient/caregiver)
- Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) assessment
- Children's C-SSRS (Since Last Visit)
- CBCL, Syndrome scale only (since last visit)
- ESRS (subscales I and II)
- ESS
- adverse events assessment
- concomitant medications
- dispense investigational medicinal product (IMP)

3. **Procedures During Administration of Investigational Medicinal Product (Double-Blind Treatment Period Inclusive of Titration Period)**

   a. Week 1 (day 7+1 day), week 2 (day 14±3 days total from baseline), week 4 (day 28±3 days total from baseline), week 5 (day 35±3 days total from baseline), and week 6 (day 42±3 days total from baseline)

The following procedures and assessments will be performed at weeks 1, 2, 4, 5, and 6:

- telephone contact (with non-recording live video)
- Clinical Global Impression of Improvement (CGI-I) (global, physician-rated)
- assessment of IMP accountability/compliance/supply
- adverse events assessment
- concomitant medications
- evaluation/adjustment of IMP dose

b. Week 3 (day 21±3 days total from baseline) and week 7 (day 49±3 days total from baseline)

The following procedures and assessments will be performed at weeks 3 and 7:

- vital signs measurements and weight
- 12-lead ECG
- urine drug screen (week 3 only)
- urine pregnancy test
- Caregiver Global Impression of Improvement (CaGI-I) (global, caregiver rated). The CaGI-I is to be completed before all other investigator-rated scales during visits where CaGI-I is collected.
- Patient Global Impression of Improvement Scale (PGI-I) (global, patient/caregiver). The PGI-I is to be completed before all other investigator-rated scales during visits where PGI-I is collected.
- Children's C-SSRS (Since Last Visit)
- CBCL, Syndrome scale only (since last visit)
- ESRS (subscales I and II)
- ESS
- CGI-I and CGI-S (global, physician rated)
- dispense/collect IMP

  During the week 3 visit, the last dose bottle is to be returned to the patient in order to take 1 last tablet in the evening to complete the week 3 dosing for that day. Refer to the pharmacy manual for further details.

- assessment of IMP accountability/compliance/supply

- adverse events assessment
- concomitant medications
- evaluation/adjustment of IMP
- contact RTSM

4. **Procedures During Administration of Investigational Medicinal Product (Maintenance Period)**

a. Week 9 (day 63±3 days total from baseline) and week 12 (day 84±3 days total from baseline)

The following procedures and assessments will be performed at weeks 9 and 12:

- vital signs measurements and weight
- urine drug screen (week 9 only)
- urine pregnancy test (week 12 only)
- MD-CRS part I video recording and investigator assessment
- MD-CRS part II video recording and investigator assessment
- CaGI-I (global, caregiver rated)
- CGI-I and CGI-S (global, physician rated)
- PGI-I (global, patient/caregiver)
- UHDRS-TMS
- Children's C-SSRS (Since Last Visit)
- CBCL, Syndrome scale only (since last visit)
- ESRS (subscales I and II)
- ESS
- dispense/collect IMP
- assessment of IMP accountability/compliance/supply
- adverse events assessment
- concomitant medications
- contact RTSM

b. Week 15 (day 105±3 days total from baseline) or early termination (ET)

The following procedures and assessments will be performed at week 15 or ET:

- vital signs measurements (including orthostatic blood pressure) and weight
- physical examination
- neurological examination

- height
- 12-lead ECG
- [redacted]
- clinical laboratory tests (chemistry, hematology, and urinalysis)
- urine drug screen
- β-HCG serum pregnancy test (for females aged 12 years or older of childbearing potential)
- MD-CRS part I video recording and investigator assessment
- MD-CRS part II video recording and investigator assessment
- CaGI-I (global, caregiver rated)
- CGI-I and CGI-S (global, physician rated)
- PEDI-CAT (ADL, caregiver completed, content-balanced version)
- PedsQL (QoL, patient/caregiver)
- PGI-I (global, patient/caregiver)
- UHDRS-TMS
- Children's C-SSRS (Since Last Visit)
- CBCL, full version (since last visit) (Competence and Syndrome)
- ESRS (subscales I and II)
- ESS
- collect IMP
- assessment of IMP accountability/compliance/supply
- adverse events assessment
- concomitant medications
- obtain reason for early termination (if applicable)
- contact RTSM

5. **Follow-Up (Weeks 16 and 17)**

   a. Week 16/End of Study follow-up visit (1 week±2 days total from the week 15/ET visit)

The following procedures and assessments will be performed at the week 16 follow-up visit:

- vital signs measurements and weight
- 12-lead ECG (if there is an abnormality at the week 15/ET visit)

- clinical laboratory tests (chemistry, hematology, and urinalysis) (if there is an abnormality at the week 15/ET visit)
- urine drug screen
- urine pregnancy test
- MD-CRS part I video recording and investigator assessment
- MD-CRS part II video recording and investigator assessment
- CaGI-I (global, caregiver rated)
- CGI-I and CGI-S (global, physician rated)
- PGI-I (global, patient/caregiver)
- Children's C-SSRS (Since Last Visit)
- CBCL, Syndrome scale only (since last visit)
- ESRS (subscales I and II)
- ESS
- adverse events assessment
- concomitant medications

b. Week 17 follow-up visit (2 weeks±2 days total from week 15 visit, or 2 weeks after ET visit)

The following procedures and assessments will be performed at the week 17 follow-up visit:

- telephone contact
- adverse events assessment
- concomitant medications

6. **Unscheduled Visits**

An unscheduled visit may be performed at any time during the study at the patient's or parent's/caregiver's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

Procedures performed during unscheduled visits may include any of the following:

- telephone contact (at the investigator's discretion)
- evaluation/adjustment of IMP
- vital signs measurements and weight
- physical examination (at the investigator's discretion)
- neurological examination (at the investigator's discretion)
- 12-lead ECG (at the investigator's discretion)

- clinical laboratory tests (chemistry, hematology, and urinalysis) (at the investigator's discretion)
- β-HCG serum pregnancy test (for females aged 12 years or older of childbearing potential) (at the investigator's discretion)
- MD-CRS part I video recording and investigator assessment
- MD-CRS part II video recording and investigator assessment
- CaGI-I (global, caregiver rated)
- CGI-I and CGI-S (global, physician rated)
- PEDI-CAT (ADL, caregiver completed, content-balanced version)
- PedsQL (QoL, patient/caregiver)
- PGI-I (global, patient/caregiver)
- UHDRS-TMS
- CBCL, Syndrome scale only (since last visit)
- ESRS (subscales I and II)
- ESS
- Children's C-SSRS (Since Last Visit) (at the investigator's discretion)
- CBCL, Syndrome scale only (since last visit) (at the investigator's discretion)
- ESRS (subscales I and II) (at the investigator's discretion)
- ESS (at the investigator's discretion)
- dispense/collect IMP (at the investigator's discretion)
- assessment of IMP accountability/compliance/supply (at the investigator's discretion)
- [redacted]
- adverse event assessment
- concomitant medications

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 Good Clinical Practice (GCP) guidelines; noncompliance to IMP administration; and 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 coronavirus disease 2019 (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 that 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.

For COVID-19 updates, refer to Appendix M.

APPENDIX E. ETHICS

Informed Consent

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 (ICF) 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. Patients who started the study as minors and reached the age of majority during the study should sign the adult ICF.

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

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 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 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 screening
- 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 parent(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 10. Investigators are encouraged to contact the medical monitor for any questions regarding the medications listed below.

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 corrected for heart rate (QTc) prolongation or that is a known strong cytochrome P450 inhibitor.

Prohibited medications that are associated with QTc prolongation are listed in Table 11.

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

Table 10: Allowed Medications

Generic/Drug class	Condition
Stable medications allowed according to inclusion/exclusions criteria	
Hormonal birth control	Must be receiving stable treatment (including dose) for at least 3 months before screening 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 and anticipated to remain stable (dose and frequency) within the study duration
Benzodiazepines, trihexyphenidyl, baclofen (oral and intrathecal), tizanidine, muscle relaxants, gabapentin, levetiracetam, carbamazepine, topiramate, and other anticonvulsants, neuroleptics (oral), typical and atypical antipsychotics, and metoclopramide	Dosing must have been stable for at least 4 weeks before screening 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 botulinum neurotoxin (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, under the guidance, supervision, or prescription of a clinician.

Table 10: Allowed Medications (Continued)

Generic/Drug class	Condition
Additional medications allowed with pre-approval from medical monitor	
Albuterol, levalbuterol	Asthma
Guaifenesin	Cold symptoms
Antihistamines	Allergies
Melatonin	Insomnia
Allowed strong CYP2D6 inhibitors[a]	
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 4.
Note: Changes to the allowed medications may be permitted in the context of this study if pre-approved by the medical monitor.
CYP=cytochrome P450; PRN=as needed.

Table 11: 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 USA
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 USA
Sparfloxacin	Antibiotic/bacterial infection	Not available in the USA
Hydroxychloroquine	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.	

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

APPENDIX I. TOTAL BLOOD VOLUME

Total blood volume to be collected for each patient in this study is approximately 40 mL (at maximum). Blood draw volumes and ranges (in mL) are depicted in Table 12.

Table 12: Total Blood Volumes

Test	Screening	Week 15/ET	Week 16/EOS	Unscheduled
[redacted]		[redacted]		[redacted])
Chemistry	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)
CYP2D6 genotyping	3.0-5.0			
β-HCG	1.25-3.5	1.25-3.5		(3.5)
Prothrombin/INR	4.5	4.5	(4.5)	(4.5)
Total volume (mL) per patient per visit	**18.5**	**21.5**		

CYP2D6=cytochrome P450 2D6; EOS=end of study; β-HCG=Beta-human chorionic gonadotropin; INR=International Normalized Ratio.
Notes: Values in parentheses indicate possible blood draws. Blood draws at week 16/EOS and unscheduled visits are optional.
[redacted]

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, the following:

- 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 [redacted] 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 the 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 a serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2).

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] test 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 (eg, results of centrally read MD-CRS part II items will not be shared with the investigators). 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, and videos) 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 (United States) 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 or phone), 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 acknowledgment 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
- case report forms for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, and electronic diary)
- safety reports
- financial disclosure reports/forms

- reports of receipt, use, and disposition of the IMPs
- 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 the 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 the following 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 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. The site will be allowed to conduct remote assent and consent by phone. Site will obtain and document a verbal confirmation from patient and parent/legally acceptable representative that they received this information and understood it. The 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

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 see patients at the investigational site.

Remote visits will allow collecting the following clinician-rated scales:

- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Clinical Global Impression of Improvement (CGI-I)
- Clinical Global Impression of Severity (CGI-S)
- Part I of the Extrapyramidal Symptom Rating Scale (subscales I and II) [ESRS].

It will further allow a visual confirmation of a patient's condition using non-recording live video and assessment of any new adverse events, as possible, depending on patient cooperation and the communication platform being in good working order. The remote visit will not allow for fully completing performance outcome assessments that require physical examinations, including those required for the Movement Disorder-Childhood Rating Scale (MD-CRS), Unified Huntington's Disease Rating Scale (UHDRS), or ESRS scales. 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-Total Motor Score (TMS) and ESRS 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 remote visit will not allow for measuring vital signs or obtaining an electrocardiogram (ECG) or urine beta chorionic gonadotropin (β-HCG) test, unless a home nursing vendor is at the patient's home to provide that service where available.

The week 3 and week 7 visits can be completed as remote visits if safety assessments (specifically vital signs, ECG, C-SSRS, and β-HCG test, if relevant) can be performed within a reasonable time from visit (approximately 2 weeks).

The week 9 and week 12 visits can be completed as remote visits if the previous vital signs and ECGs were acceptable as per protocol requirements. Any other required safety assessments (eg, C-SSRS and β-HCG test, if relevant) that are not completed during a remote visit should be completed within 2 weeks of the remote visit.

If patient misses the week 15 visit and is approved by the medical monitor to have a remote visit and continue on drug, and if patient cannot arrive at site within 3 weeks, a telephone call will be added to assess patient's condition (ie, adverse event, tolerability, sufficient investigational medicinal product [IMP]).

The week 16 visit can be completed as a remote visit.

The test and placebo IMP (as applicable) will continue to be administered at home. Following the consent of the patient or parent(s)/legally acceptable representative, IMP will be shipped to patients if they or their parent/legally acceptable representative cannot visit the site to collect IMP. All shipping arrangements will be the site's responsibility and will occur between site and patient or as a direct-to-patient shipment from the site to patient coordinated by the sponsor's third party shipping vendor, where available, and according to local practices and regulations.

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. For example, if central lab samples cannot be collected for safety assessments, sites may have patients visit a local reference laboratory, or a home service may visit home, to perform the assessments.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the original protocol instructions will be followed whenever the new instructions are not required.

Section 4.3. Withdrawal Criteria and Procedures for the Patient

Patients who cannot complete the required safety assessments within a reasonable time from visit (approximately 2 weeks for the week 3 and week 7 visits) will be early terminated from study; specifically, these are the vital signs, ECG, C-SSRS, and β-HCG tests at weeks 3 and 7.

Patients who cannot reach the site for a week 15 visit will be allowed to remain on drug for an additional 4 weeks. After 3 weeks, if the patient has not yet completed the in-clinic week 15 visit, the investigator will perform another remote visit to check on the patient's condition. The contract research organization (CRO) will assess with the site if their patient can come to complete the week 15 visit in the next week. If not, the sponsor will either allow another extension or the patient will be early terminated from the study.

Section 4.5. Rescreening

Patients who screen fail or terminate early from the study due to emergency circumstances (such as coronavirus disease 2019 [COVID-19] restrictions) may be allowed to re-screen/re-enter (respectively) the study at a later date, depending on the circumstances. Each case should be referred to the medical monitor and approved in advance. Patients re-entering the study will be manually assigned to their initial treatment group. Patients will have to redo the entire study from the start, aside from the blinded CYP2D6 genotyping; these results will carried over from the first participation.

Section 5.9. Randomization and Blinding

Patients re-entering the study will be manually assigned to their initial treatment group by the RTSM unblinded vendor. Blinding will be maintained for the patient, investigator, and sponsor as described above; the only information that will be available is that the patient was assigned to the same treatment group as previously.

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), patients will be able to complete the efficacy scales at home using the iPhone. The results of the questionnaires completed via patient's iPhone will be transferred to the case report form (CRF) per the usual process. Scales collected as paper forms will be stored in patient source file and entered to CRF manually once the CRF has been adapted appropriately.

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), patients will be allowed to obtain vital signs and ECGs using local clinics (primary health care provider) or home nursing service, where available.

Safety measurements such as vital signs/ECG/β-HCG/C-SSRS are mandatory for weeks 3 and 7 (during titration) and part of the week 15/16 assessments.

To increase safety assessments, and in anticipation that patients may need to significantly delay their week 15 visit, investigators may collect several safety assessments at week 12 that are currently not part of the schedule of activities, but are possible using 'unscheduled' visits: physical examination, neurological examination, 12-lead ECG, and chemistry/hematology/urinalysis laboratory tests. These safety measurements are at the investigator's discretion.

Section 7.5.2.1. Beta-Human Chorionic Gonadotropin Tests

If an in-clinic visit is replaced by a remote visit, all efforts will be done to collect the β-HCG (eg, at local laboratory or by sending urine β-HCG sticks to the patient and parent/legally acceptable representative, so these can be assessed at home).

Section 7.5.2.2. Urine Drug Screen

If an in-clinic visit is replaced by a remote visit, urine drug screen samples will not be collected, until a next in-clinic visit is possible.

Section 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, etc), will be described in the appropriate sections of the clinical study report (CSR) as applicable.

Appendix D. Quality Control and Quality Assurance

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, etc), will be described in the appropriate sections of the CSR as applicable.

Study Monitoring

In case of an emergency situation (eg, the COVID-19 pandemic), where study monitors may not be able to access the investigational centers for on-site visits, sites will be monitored remotely where allowed and in accordance with the local regulations. Additional 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 E. Ethics

A COVID-19 addendum informed consent will be created to inform patients of the planned changes. The site will be allowed to conduct remote assent and consent by phone. Site will obtain and document a verbal confirmation from patient and parent/legally acceptable representative that they received this information and understood it. The 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.

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. The medical monitor should be consulted for further advice.