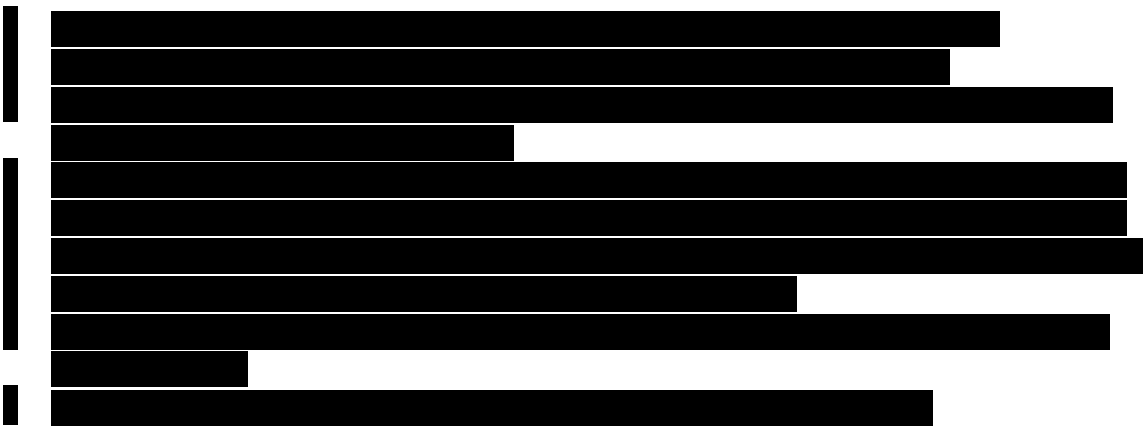


Safety Endpoints:

- Incidence of adverse events
- Observed values and changes from baseline in vital signs
- Observed values and change from baseline in the Children's Depression Inventory, Second Edition (CDI-2), Parent and Self-report Profiles
- Observed values in the Children's Columbia-Suicide Severity Rating Scale (C-SSRS)
- Observed values in electrocardiogram (ECG) parameters and shifts from screening for clinically significant abnormal findings
- Observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis)

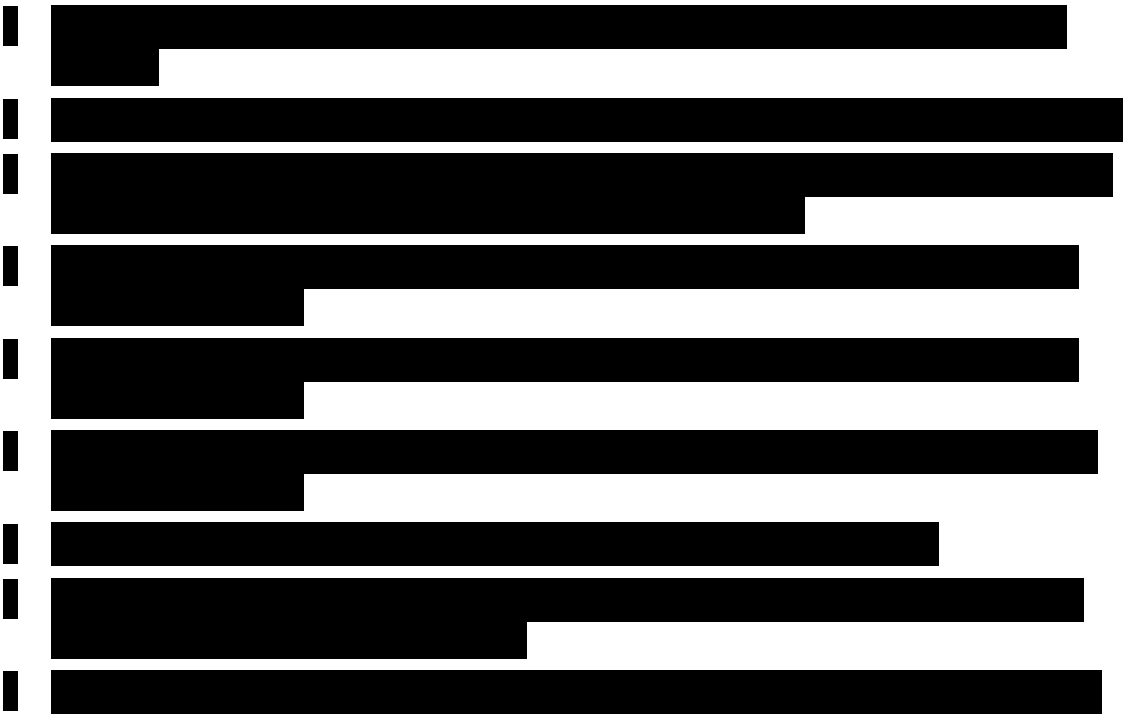
Pharmacokinetic Endpoint:

- The pharmacokinetics of the alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ) metabolites of TEV-50717, and other metabolites (as needed), will be explored based on sparse sampling at week 12.

General Design and Methodology:

This is a Phase 2/3, randomized, double-blind, placebo-controlled, parallel group study in which patients with tics associated with TS will be invited to participate. Patients who qualify for the study will be centrally randomized in a 1:1 ratio (stratified by age at baseline [6 to 11 years, 12 to 16 years]) to receive either TEV-50717 or placebo. Throughout the study, patients will interact regularly with investigative site personnel, in clinic and by telephone, for the evaluation of safety, tic severity, and behavioral status (in clinic only). The target dose for each patient receiving TEV-50717 will be based on 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 based on blinded assessment of CYP2D6 genotype at baseline. CYP2D6 status will be used by Interactive Response Technology (IRT) for randomization into the study. The dose of IMP for each patient will be titrated to an optimal level followed by maintenance therapy at that dose. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT. The overall treatment period will be 12 weeks in duration, including a titration period of 7 weeks, a maintenance period of 5 weeks, followed by a washout period of 1 week [redacted]. For the YGTSS, input from the caregiver/adult is required. For both the TS-PGII and [redacted], input from the caregiver/adult is permitted. For all other scales, for children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or defined by the scale; for children over 13 years of age, caregiver/adult involvement is strongly encouraged.

Abbreviation or Specialist Term	Explanation
ECG	electrocardiogram
ePRO	electronic patient-reported outcome
ET	early termination visit
FDA	Food and Drug Administration [United States]
GCP	Good Clinical Practice
GPSP	Global Patient Safety and Pharmacovigilance
[redacted]	[redacted]
C&A-GTS-QOL	Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life
HD	Huntington disease
IB	Investigator's Brochure
ICH	International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IDMC	Independent Data Monitoring Committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IMP	investigational medicinal product
IND	Investigational New Drug [Application]
IRT	Interactive Response Technology
ITT	intent-to-treat
LDH	lactate dehydrogenase
LSO	local safety officer
MA	Marketing Authorization
MAOI	monoamine oxidase inhibitor
MINI Kid	Mini International Neuropsychiatric Interview For Children and Adolescents (version 6.0)
mITT	Modified Intent-to-Treat
[redacted]	[redacted]
NA	not available
NDA	New Drug Application
NOAEL	no-observed-adverse-effect level
OCD	obsessive-compulsive disorder
PD	pharmacodynamic
PGx	pharmacogenetics



2.3.4. Safety Endpoints

The safety endpoints for this study are as follows:

- incidence of adverse events
- observed values and changes from baseline in vital signs
- observed values and change from baseline in the Children's Depression Inventory, Second Edition (CDI-2), Parent and Self-report Profiles
- observed values in the Children's Columbia-Suicide Severity Rating Scale (C-SSRS)
- observed values in electrocardiogram (ECG) parameters and shifts from screening for clinically significant abnormal findings
- observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis)

2.3.5. Pharmacokinetic Endpoint

The pharmacokinetics of the α- and β-HTBZ metabolites of TEV-50717, and other metabolites (as needed), will be explored based on sparse sampling at week 12.

3. STUDY DESIGN

3.1. General Design and Study Schema

3.1.1. Overall Design and Screening Period

This is a Phase 2/3, randomized, double-blind, placebo-controlled, parallel group study in which patients with tics associated with TS will be invited to participate. Patients who qualify for the study will be centrally randomized in a 1:1 ratio (stratified by age at baseline [6 to 11 years, 12 to 16 years]) to receive either TEV-50717 or placebo. Throughout the study, patients will interact regularly with investigative site personnel, in clinic and by telephone, for the evaluation of safety, tic severity, and behavioral status (in clinic only). The target dose for each patient receiving TEV-50717 will be based on body weight and 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 based on blinded assessment of CYP2D6 genotype at baseline. CYP2D6 status will be used by Interactive Response Technology (IRT) for randomization into the study. The dose of IMP for each patient will be titrated to an optimal level followed by maintenance therapy at that dose. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT (Table 2). The overall treatment period will be 12 weeks in duration, including a titration period of 7 weeks, a maintenance period of 5 weeks, followed by a washout period of 1 week. [redacted] For the YGTSS, input from the caregiver/adult is required. For both the TS-PGII and [redacted] input from the caregiver/adult is permitted. For all other scales, for children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or defined by the scale; for children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. It should be noted that the CDI-2 has individual parent and child questionnaires.

Patients who complete the study may be eligible to begin participation in an open-label safety extension study (TV50717-CNS-30047) after the end of the washout period. At the week 13 visit, patients may choose to enter Study TV50717-CNS-30047 (on that day), or they will have an additional week to make a decision and return for day 1. Patients not participating in Study TV50717-CNS-30047 will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP).

3.1.2. Screening Period

The screening period in this study is up to 31 days. After informed consent/assent, depending on the child's age, 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, and 12-lead ECG, along with rating scales to assess severity, frequency, and impairment of tics and comorbid TS symptoms and behavioral status.

At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is felt to be too burdensome for the patient. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits. Patients who have received comprehensive behavioral intervention for tics (CBIT) for TS or cognitive behavioral therapy (CBT) for obsessive-compulsive disorder (OCD) may participate in this study as long as therapy was completed at least 4 weeks prior to screening. Patients will return to the clinic on day 1 to perform baseline procedures and to reconfirm eligibility. Patients may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

3.1.3. Titration Period

During the titration period (7 weeks), patients who remain eligible for participation in the study will be randomized in a 1:1 ratio stratified by age (6 to 11 years, 12 to 16 years) at the baseline visit (day 1), and that evening (ie, after the study visit) will receive 6 mg of blinded IMP with food. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. The titration scheme and maximum dose will be determined by body weight and CYP2D6 impairment status at baseline, as shown in Table 2. Patients and their caregiver/adult will interact weekly with the clinical research staff, either by telephone contact or clinic visit from week 1 through week 7 of the titration period, in order to evaluate safety and establish a dose of IMP that optimally reduces tics and is well tolerated (optimal dose). Safety 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.

In-person (in-clinic) study visits will be scheduled at weeks 2, 4, and 6, and telephone contacts will be scheduled for weeks 1, 3, 5, and 7 in order to assess tic severity and adverse events. The dose of the IMP should be increased on a weekly basis until one of the following criteria is met:

- The investigator determines that there has been a clinically meaningful reduction in tics, as indicated by a sustained reduction in the TS-CGI
- The patient experiences a protocol-defined “clinically significant” adverse event (defined as an adverse event that is related to study medication and is either moderate or severe in intensity or meets the criteria for a serious adverse event).
- The maximum allowable dose is reached, based on the patient’s weight and CYP2D6 impairment status at baseline.

Although dose adjustments can be made up to and including the week 7 telephone call, if a stable dose is reached before then, the patient should continue on that dose (ie, the dose should not be increased further) for the remainder of the titration period and throughout maintenance dosing, unless there is a change in symptoms during the titration period. If a patient experiences a “clinically significant” adverse event attributable to the IMP, the investigator will determine if a dose reduction or suspension is necessary. If the determination that a patient requires a dose reduction or suspension is made during a telephone contact, an unscheduled clinic visit should be conducted as soon as practicable thereafter.

Dose adjustments should be made based on all available information, including the patient and caregiver/adult reports of adverse events and tic reduction, the clinical assessment of safety and

3.3. Primary and Secondary Efficacy Measures and Time Points

A description of the efficacy measures is provided in Section 6.

3.3.1. Primary Efficacy Measure and Time Points

YGTSS (to calculate TTS): Screening; baseline; and weeks 2, 4, 6, 9, 12, and 13.

3.3.2. Key Secondary Efficacy Measures and Time Points

1. TS-CGI: baseline and weeks 2, 4, 6, 9, 12, and 13
2. TS-PGII: baseline and weeks 2, 4, 6, 9, 12, and 13
3. C&A-GTS-QOL ADL subscale: baseline, week 6, and week 12

3.3.3. Exploratory Measures and Time Points

[redacted]

3.4. Safety Measures and Time Points

- adverse events and concomitant medications: from the signing of the informed consent/assent, depending on the child's age, as appropriate, through follow-up, inclusive of all visits and telephone contacts
- physical examination: screening and week 12
- neurological examination: screening and week 12
- vital signs: screening; baseline; and weeks 2, 4, 6, 9, 12, and 13
  Note: orthostatic blood pressure (BP) and pulse at baseline and weeks 4 and 12
- MINI Kid: screening

- Children's C-SSRS
  - Baseline/screening scale: screening
  - Since Last Visit [SLV] scale: baseline and weeks 2, 4, 6, 9, 12, and 13
- CDI-2 (Parent and Self-Report versions): screening; baseline; and weeks 2, 4, 6, 9, 12, and 13
- 12-lead ECG: screening; baseline; and weeks 4, 6, and 12
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): screening and week 12
- pregnancy testing: screening, baseline, and weeks 4 and 12
- drug screen: screening and week 12

A description of the safety measures is provided in Section 7.

3.5. Pharmacokinetic Measures and Time Points

Blood samples will be obtained for the measurement of plasma concentrations of TEV-50717 (deutetrabenazine), α-HTBZ, β-HTBZ, and other metabolites, as needed. Blood sampling for pharmacokinetic analysis will be performed at the week 12 visit. 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. The time between samples should be maximized in order to provide the most useful information.

A description of the pharmacokinetic measures is provided in Section 8.

3.6. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Patients will be randomly assigned to receive treatment with TEV-50717 or matching placebo in a 1:1 ratio stratified by age at baseline (6 to 11 years, 12 to 16 years). Patients and investigators will remain blinded to treatment assignment during the study.

Patients will be centrally randomly assigned to the treatment groups by means of a computer-generated randomization list after confirmation of all eligibility criteria. The creation of the randomization list will be under the responsibility and oversight of Syneos Health.

In addition, the sponsor's clinical personnel and all vendors (with exception of the IRT vendor and the bioanalytical sample analysis vendor) involved in the study will be blinded to the IMP identity until the database is locked for analysis and the treatment assignment revealed. After unblinding of this study, the study site may remain blinded to patient treatment assignments until completion of the safety extension study TV50717-CNS-30047.

The randomization list and treatment will be assigned to the relevant treatment groups through a qualified service provider (ie, via IRT). The generation of the medication list and management of the IRT system will be done by a qualified service provider under the oversight of Nuvelution TS Pharma.

The staff member at the investigational center who will dispense the IMP will not know the treatment given to each patient.

3.7. Maintenance of Randomization and Blinding

3.7.1. Randomization

Patient randomization codes will be maintained in a secure location within Syneos Health, Biometrics. At the time of analysis, when treatment codes are needed, the Syneos Health statistician assigned to the study will make a request to unblind and will receive the unblinded codes.

3.7.2. Blinding/Unblinding

Pharmacokinetic data may be assessed during the study. For patients who have pharmacokinetic sample bioanalysis and/or data analysis conducted, the individuals responsible for sample bioanalysis and other responsible personnel will know who received IMP and who received placebo during the study (of those patients only). Personnel responsible for bioanalysis will be provided with the randomization code in order to facilitate the analysis. However, the personnel responsible for bioanalysis and pharmacokinetic data analysis will not have access to clinical safety and efficacy data, will not have any interaction with study personnel, and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to an individual patient's concentration data).

For information about personnel who may be aware of treatment assignments, see Section 3.6. 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 or 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. Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) and/or pharmacist(s) at the study center via the IRT system. If possible, the sponsor should be notified of the event prior to breaking of the code. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's drug code assignment should not be revealed. Breaking of the treatment code can always be performed by the site without prior approval by the sponsor.

When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded onto the case report form (CRF). However, if a patient is unblinded by mistake, the investigator should discuss with the medical monitor whether or not the patient should be withdrawn. 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. Treatment assignment should not be recorded in any study documents or source document.

In blinded studies, for adverse events that are defined as: suspected unexpected serious adverse reactions (SUSARs) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the treatment code be revealed (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an

Table 1: Study Procedures and Assessments (Continued)

	Screening	BL[a]	Titration							Maintenance		Follow-up		U
Study week[b]	**Up to 31 days**	**Day 1[c]**	**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/ET[d] (Day 84)**	**13 (Day 91**	**14[e] (Day 98)**	
Visit window (days)		**0 days**	**±3 days**									**±3 days from Week 12**		
MINI Kid[p,q]	X													
CDI-2 (Parent and Self-report)[r]	X	X		X		X		X		X	X	X		X[j]
C-SSRS (Children's Baseline/Screen)[q]	X													
C-SSRS (Children's Since Last Visit)[q]		X		X		X		X		X	X	X		X[j]
YGTSS[s,t]	X	X		X[u]		X		X[u]		X[u]	X	X[u]		
TS-CGI[t]		X		X		X		X		X	X	X		
TS-PGII[t]		X		X		X		X		X	X	X		
[redacted][t]		X		X		X		X		X	X	X		
[redacted]		X		X		X		X		X	X	X		
[redacted]		X						X[v]			X	X[v]		
C&A-GTS-QOL[q]		X						X			X			
Dispense IMP[w]		X[x]		X[x]		X[x]		X[y]		X[y]				X[j]
Collect IMP				X		X		X		X	X			X[j]
Assess IMP accountability/compliance/supply			X[z]	X	X[z]	X	X[z]	X	X[z]	X	X			X[j]
Assess adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[aa]	X	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]	X[aa]

[a] The baseline visit will occur on the same day as the scheduled first dose of the IMP (day 1).

- measure weight (Note: Weight must be measured with shoes and outerwear off)
- inquire about adverse events
- review concomitant medications

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

- measure height
- perform physical examination
- perform neurological examination
- perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.)
- perform clinical laboratory tests, including chemical, hematological, and urine analyses
- perform a urine/serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires:
  - CDI-2, Parent and Self-report (Note: Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.)
  - C-SSRS (children's SLV; Note: Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.)
- dispense additional IMP and patient diary, if applicable
- collect used and unused IMP blister packs
- assess drug accountability/compliance/supply

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

change have face validity and have been shown to correlate with disability for a number of chronic conditions.

6.2.3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.4. Child and Adolescent Gilles de la Tourette Syndrome-Quality of Life Scale

The C&A-GTS-QOL is administered at baseline, week 6, and week 12. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

The C&A-GTS-QOL is a 27-item questionnaire specific to TS patients that asks the patient to assess the extent to which their quality of life is impacted by their symptoms. The C&A-GTS-QOL contains 6 subscales (cognitive, coprophenomena, psychological, physical, obsessive-compulsive, and ADL) and uses a 5-point Likert scale ranging from no problem to extreme problem. Patients will also be asked how satisfied they feel overall with their life at that moment by using a VAS scale between 0 and 100 (Su et al 2017).

A reference sample is provided in Appendix K.

6.2.5. [redacted]

[redacted]

6.2.6. [redacted]

[redacted]

[redacted]

[redacted]

7.1.2. Recording and Reporting Adverse Events

For recording of adverse events, the study period is defined for each patient as that time period from signature of the informed consent/assent form to the end of the follow-up period. For this study, the follow-up period for recording of adverse events is defined as 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of IMP for patients who will not roll over into Study TV50717-CNS-30047.

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 (see Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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

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

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding 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 1 of the following:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the IMP

The relationship of an adverse event to the IMP is characterized as follows:

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

7.1.5. Serious Adverse Events

An additional blood sample for the measurement of IMP concentration should be collected, if possible, from each patient experiencing a serious adverse event leading to discontinuation of IMP at any time during the study. If study center personnel are unable to obtain a blood sample in a timely fashion, this should be discussed with the medical monitor to determine whether the sample still needs to be obtained.

For recording of serious adverse events, the study period is defined for each patient as the time period from signature of the informed consent/assent form to the end of the follow-up period, as defined in Section 7.1.2. If the investigator becomes aware of serious adverse events occurring in a patient after the end of the follow-up period, the serious adverse events should be reported to the sponsor 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 a 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 which 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 informed consent form 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:

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

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

7.1.5.2. Expectedness

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

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

The sponsor's 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 by the investigator according to the instructions provided on the serious adverse event form. 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 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 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 disease.

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

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/Syneos Health for submission to the competent authorities, IEC/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 a SUSAR, only the LSO/Syneos Health will receive the unblinded report for regulatory submission; the others will receive a blinded report.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.3).

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 regulatory 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 current study participants of new findings

7.2.1. Mini International Neuropsychiatric Interview for Children and Adolescents

Select MINI Kid modules are administered at screening only. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

The MINI Kid is a short questionnaire to be administered by a trained clinician. The MINI Kid assesses symptoms of psychiatric disorders as outlined in the International Classification of Diseases-10 and the DSM in children 6 to 17 years of age by self-report. For children under 13 years old, the patient may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale, and the caregiver/adult is encouraged to participate when needed. The MINI Kid version 6 is composed of 24 modules overall, and questions are largely yes-or-no questions. The current study will focus on 8 modules: Major Depressive Episode (Module A), (Hypo) Manic Episode (Module D), OCD (Module J), Alcohol Dependence/Abuse (Module L), Substance Dependence/Abuse (Non-alcohol; Module M), ADHD (Module O), Conduct Disorder (Module P), and Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).

A reference sample is provided in Appendix C.

7.2.2. Columbia-Suicide Severity Rating Scale

The C-SSRS children's baseline/screening scale assesses past and current suicidal ideation and behaviors to determine suicide risk and is administered at screening. The C-SSRS children's SLV scale is administered at baseline and at weeks 2, 4, 6, 9, 12, and 13. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The C-SSRS is an interview by trained study personnel.

Suicidal ideation

- Patients with a positive C-SSRS suicidal ideation score on either items 1 or 2 or a change on the CDI-2 Parent or Self-Report Profiles consistent with increasing depressive symptoms must be 1) discussed with the 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 and adolescent psychiatrist or licensed child/adolescent mental health provider is advised, followed by close ongoing monitoring.
- If patients endorse or report a C-SSRS suicidal ideation level of 3, 4, or 5, subjects will be evaluated immediately by the study investigator and referred for psychiatric evaluation. The medical monitor will be immediately consulted. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to this change in C-SSRS and/or increased depressive symptoms, IMP will be immediately discontinued and the patient 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

related diseases. The final list of genes to be evaluated will be determined at the time of analysis to be able to account for the most current research.

9.5.3. Exploratory Endpoints

Exploratory endpoints for this study are as follows:

9.5.4. Planned Method of Analysis

The mITT analysis set (see Section 9.2) will be used for all efficacy analyses. Summaries will be presented by treatment group.

9.5.4.1. Primary Efficacy Analysis

The primary analysis will be a mixed-model, repeated-measures with the change in the TTS as the dependent variable. The model will include fixed effects for treatment group, week (5 levels: weeks 2, 4, 6, 9, and 12), and the treatment group by week interaction. The baseline TTS, region, and age group at baseline (2 levels: 6 to 11 years, 12 to 16 years) will be included as covariates. The unstructured covariance matrix for repeated observations within patients will be used. In case that the model does not converge, the Maximum-Likelihood estimation method will be used instead of the default Restricted Maximum-Likelihood. If the model still does not converge, then a simpler covariance structure with fewer parameters will be used, according to the following order: Heterogeneous Autoregressive (1), Heterogeneous Compound Symmetry, Autoregressive (1), and Compound Symmetry. The least squares means of the change in TTS from baseline at week 12 will be compared (the active treatment arm and the placebo arm) using a 2-sided test at the alpha=0.05 level of significance.

In addition, actual values and changes in the TTS from baseline to each visit will be summarized using descriptive statistics.

9.5.4.2. Sensitivity Analysis

Sensitivity analyses for missing data, the statistical model, and the increase in sample size will be provided in the statistical analysis plan.

9.5.4.3. Key Secondary Efficacy Analyses

A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory. The change in the TS-CGI (1) and C&A-GTS-QOL ADL subscale (3) scores from baseline to week 12 will be summarized and analyzed in the same fashion as the primary analysis, with the exception that the baseline value of the given endpoint will be included as the covariate. TS-PGII (2) will be analyzed using a Cochran-Mantel-Haenszel row mean score test with a modified ridit scoring that controls for age group.

9.5.4.4. Exploratory Analyses

[redacted]

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

Observed values in the C-SSRS and observed values and changes from baseline in the CDI-2 (Parent and Self-report versions) will be presented by treatment group for all patients.

9.8. Pharmacokinetic Analysis

The pharmacokinetic endpoint is listed in Section 2.3.5. Samples collected for pharmacokinetic analysis will be quantified for α-HTBZ and β-HTBZ of TEV-50717, and other metabolites (as needed), will be analyzed using population pharmacokinetic techniques. Analysis methods will be detailed in a separate population pharmacokinetic analysis plan. Exploratory pharmacokinetic/PD analysis may be performed on PD/safety endpoints.

9.9. Planned Interim Analysis

No interim analysis is planned for this study.

9.10. Reporting Deviations from the Statistical Plan

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

12. ETHICS

Details of compliance with regulatory requirements and applicable laws are provided in Section 1.6.

12.1. Informed Consent/Assent

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

A personally signed and dated informed consent form will be obtained from parent/legally acceptable representative, and a signed and dated assent, depending on the child's age, as appropriate, will be obtained from each patient (if the patient is able) before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained; according to national and local IEC/IRB requirements. The forms will be signed and dated also by the person who conducted the informed consent discussion. The investigator will keep the original informed consent/assent forms, depending on the child's age, as appropriate, and copies will be given to the patients. It will also be explained to the patients (and parent/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.

12.2. Competent Authorities and Independent Ethics Committees/Institutional Review Boards

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

12.3. 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 CRFs 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 transcribed to the CRF. 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.

Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. It should be noted that the CDI-2 has individual parent and child questionnaires.

Patients who complete the study may be eligible to begin participation in an open-label safety extension study TV50717-CNS-30047 after the end of the washout period. At the week 13 visit, patients may choose to enter Study TV50717-CNS-30047 (on that day), or they will have an additional week to make a decision and return for day 1. Patients not participating in Study TV50717-CNS-30047 will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP).

Screening period (up to 31 days): After informed consent/assent, depending on the child's age, 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, and 12-lead ECG, along with rating scales to assess severity, frequency, and impairment of tics and comorbid TS symptoms and behavioral status.

At the discretion of the investigator, the screening visit may be divided into 2 visits if the visit length is felt to be too burdensome for the patient. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits. Patients who have received comprehensive behavioral intervention for tics (CBIT) for TS or cognitive behavioral therapy (CBT) for obsessive-compulsive disorder (OCD) may participate in this study as long as therapy was completed at least 4 weeks prior to screening. Patients will return to the clinic on day 1 for baseline procedures and to re-confirm eligibility. Patients may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

YGTSS Rater Certification: All investigators and subinvestigators who will be administering the YGTSS from screening through the end of study visit must undergo and pass a Rater Certification Program which will be provided separately from this protocol. Every effort must be made to ensure that the same certified rater administers the YGTSS to a specific patient at all visits, especially at the baseline and week 12/early termination visits. However, if due to unforeseen circumstances the same rater is absolutely unavailable to complete a visit rating, the YGTSS can be administered only by another certified individual from that study site.

Titration period (7 weeks): Patients who remain eligible for participation in the study will be randomized at the baseline visit (day 1), and that evening (ie, after the study visit) will receive 6 mg of blinded IMP with food. Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. The titration scheme and maximum dose will be determined by body weight and CYP2D6 impairment status at baseline, as shown in the tables below. Patients and their caregiver/adult will interact weekly with the clinical research staff, either by telephone contact or clinic visit from week 1 through week 7 of the titration period, in order to evaluate safety and establish a dose of IMP that optimally reduces tics and is well tolerated (optimal dose). Safety 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.

In-person (in-clinic) study visits will be scheduled at weeks 2, 4, and 6, and telephone contacts will be scheduled for weeks 1, 3, 5, and 7 in order to assess tic severity and adverse events. The dose of the IMP should be increased on a weekly basis until one of the following criteria is met:

- The investigator determines there has been a clinically meaningful reduction in tics as indicated by a sustained reduction in the TS-CGI.
- The patient experiences a protocol-defined "clinically significant" adverse event (defined as an adverse event that is related to study medication and is either moderate or severe in intensity or meets the criteria for a serious adverse event).
- The maximum allowable dose is reached based on the patient's weight and CYP2D6 impairment status at baseline.

Abbreviation or Specialist Term	**Explanation**
PND	postnatal day
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SD-809/TEV-50717	deutetrabenazine
SLV	Since Last Visit
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
Tbil	total bilirubin
TD	tardive dyskinesia
TEAE	treatment-emergent adverse event
TS	Tourette syndrome
TS-CGI	Tourette Syndrome-Clinical Global Impression
TS-PGII	Tourette Syndrome-Patient Global Impression of Impact
[redacted]	[redacted]
TTS	Total Tic Score
U	unscheduled visit
UDS	urine drug screen
ULN	upper limit of the normal range
USA	United States of America
VAS	visual analog scale
VMAT2	vesicular monoamine transporter 2
[redacted]	[redacted]
WBC	white blood cell
YGTSS	Yale Global Tic Severity Scale

efficacy by the investigator, and information from rating scales. At the end of the titration period, the patient's dose will be established for the maintenance period.

3.1.4. Maintenance Period

During the maintenance period (5 weeks), patients will continue to receive their maintenance dose, although dose reductions for adverse events are allowed. Patients will return to the clinic at weeks 9 and 12 for assessments of safety and efficacy. At week 12, patients will undergo a complete evaluation, including physical and neurological examination, safety laboratory testing, 12-lead ECG, CDI-2, and C-SSRS assessments, as well as the YGTSS, TS-CGI, TS-PGII, [redacted], [redacted], and C&A-GTS-QOL.

In addition, patients will undergo pharmacokinetic sampling at week 12.

3.1.5. Washout Period and Follow-up

All patients will discontinue IMP at the week 12 visit and will return 1 week later for evaluation of safety and tic reduction (week 13). Patients who complete the study may be eligible to begin participation in the open-label safety extension study TV50717-CNS-30047. For this study, the follow-up period is defined as 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of IMP (1 week after the end of the washout period) for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047. At the week 13 visit, patients may choose to enter Study TV50717-CNS-30047 (on that day), or they will have an additional week to make a decision and return for day 1. Patients not participating in Study TV50717-CNS-30047 will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP).

Prohibited drugs will remain the same during the washout period for patients who will participate in the open-label extension study TV50717-CNS-30047.

Patients who will not participate in the extension study (Study TV50717-CNS-30047) may begin/resume tic therapy medication after the first week of the washout period.

See Table 1 for study procedures and assessments.

See Figure 1 for study schema.

unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct, analysis, and reporting of the data.

3.7.3. Independent Data Monitoring Committee

During the conduct of this study, an IDMC will review accumulating safety data on a regular basis to ensure the continuing safety of the study patients and review of any study conduct issues.

The IDMC will be composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, such as a statistician. The IDMC will receive safety data periodically which will be presented by masked treatment groups. They will have the right to recommend modification of the study for safety reasons.

IDMC sessions can be open or closed. During open sessions, representatives of the sponsor 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).

If there is a request to unblind any individual treatment assignment, a written request from the IDMC (as a committee), signed by the IDMC chairperson, should be made to the unblinded statistician. The appropriate medical and operational personnel will be notified but will not receive the unblinded treatment information. Any use of unblinded treatment assignments should be clearly documented and reported to the sponsor at study termination.

The IDMC chairperson will communicate with Nuvelution TS Pharma in regard to issues resulting from the conduct and clinical aspects of the study. Nuvelution TS Pharma and Syneos Health 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 blinded treatment assignment are outlined in the IDMC charter.

3.8. Drugs Used in the Study

3.8.1. IMP

The IMP is a matrix formulation and is designed as a gastro-erosional tablet to be administered with food 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 regulations. TEV-50717 tablets are available in the following strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). The IMP will be supplied in 40-count blister packs. The placebo tablets and packaging will match those for TEV-50717. Each blister pack (40-count tablets per dose strength per blister pack) will contain a sufficient supply of drug until the next specified visit/telephone contact, plus overage to account for potential delays in study visits.

A more detailed description of administration procedures is given in Section 5.1.

[b] Assessment to occur at the end of the study week.
[c] Patients will be provided with a diary to record critical information on dosing. The date and time of the last dose of study medication before the week 12 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit on week 12, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary.
[d] For patients who withdraw prematurely, an early termination 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; evaluations will be as described for week 14 (Section 3.13.4.2).
[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 TV50717-CNS-30047.
[f] The screening visit may be conducted over 2 separate visits at the discretion of the investigator.
[g] Dose adjustment will be made by the investigator after telephone contact with the patient and caregiver/adult to evaluate tic reduction and adverse events.
[h] 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 5 minutes (the same position and arm should be used each time vital signs are measured for a given patient).
[i] Orthostatic BP and pulse will be measured after patient is in a standing position for at least 3 minutes.
[j] Assessment to be completed at investigator's discretion.
[k] All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.
[l] 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 AM dosing) should take their IMP dose in clinic after the first pharmacokinetic sample is collected.
[m] Patients with clinically significant laboratory abnormalities at week 12 will have those laboratory evaluations repeated at the week 13 visit.
[n] The patient's genotype for CYP2D6 will be blinded during the conduct of the study.
[o] For females who are postmenarchal or ≥12 years of age, a urine test will be administered at baseline and week 4, while a serum test will be administered at screening and week 12, and if clinically indicated.
p MINI Kid, (Children and Adolescents) modules to be used are: Major Depressive Episode (Module A), (Hypo) Manic Episode (Module D), OCD (Module J), Alcohol Dependence/Abuse (Module L), Substance Dependence/Abuse (Non-alcohol; Module M), ADHD (Module O), Conduct Disorder (Module P), and Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).
[q] For children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.
[r] Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.
[s] Input from the caregiver/adult is required.
[t] The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.
[u] Perform assessment of "Severity Ratings" of the questionnaire. Inventory portions, ie, "Motor Tic Symptom Checklist" and "Phonic Tic Symptom Checklist" do not need to be performed.
[v] Perform the Severity Ratings of OCD symptoms (Questions 1 through 10) only. Checklist does not need to be performed.
[w] Contact IRT and dispense IMP and patient diary.
[x] IMP will be dispensed in the clinic; patients will receive doses for 2 weeks (current dose level and next dose level) to cover the telephone contacts. The site will determine titration (ie, starting the next dose) for the patient by telephone. See Table 2 for baseline weight-based dosing titration.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be enrolled are not granted by sponsor or Syneos Health (see Section 11.1.2).

4.1. Patient Inclusion Criteria

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

a. Patient is 6 to 16 years of age, inclusive, at baseline.

b. Patient weighs at least 44 pounds (20 kg) at baseline.

c. Patient meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V™) diagnostic criteria for TS and, in the opinion of the investigator, patient, and caregiver/adult, the patient's active tics are causing distress or impairment.

d. Patient has a TTS of 20 or higher on the YGTSS at screening and baseline.

e. Patient is able to swallow study medication whole.

f. Patient and caregiver/adult are willing to adhere to the medication regimen and to comply with all study procedures.

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

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

i. Patient and caregiver/adult provide written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.

j. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β-HCG test at baseline or are sterile. Definitions of sterile are given in Appendix L.

k. 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 or 5 half-lives, whichever is longer after the last dose of IMP. Further details are included in Appendix L.

4.2. Patient Exclusion Criteria

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

a. Patient has a neurologic disorder other than TS that could obscure the evaluation of tics.

6.2.7. [redacted]

- 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 were identified for this study.

7.1.7. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator or sponsor. If a post-baseline QTcF value >500 msec or change from baseline >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (baseline and screening) to the average of the 3 post-baseline QTcF values. The IMP must be stopped for any confirmed post-baseline QTcF value >500 msec or increase from baseline >60 msec. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time.

In addition, a blood sample should be obtained for the measurement of IMP concentrations, if possible. 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 include adverse events, the termination 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, not the adverse event.

7.1.8. 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.

7.2. Psychometric Rating Scales

Site-administered safety scales include the MINI Kid and C-SSRS, and self-administered safety scales include CDI-2.

monitor, the consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.

Suicidal behavior

- Actual attempt:

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

- Interrupted attempt, aborted attempt, or Preparatory Acts or Behavior:

  If patients report any suicidal behavior that is interrupted, aborted, or preparatory as assessed in the C-SSRS, they will be evaluated immediately by the study 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, the consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.

A reference sample is provided in Appendix E.

7.2.3. Children's Depression Inventory, Second Edition

The CDI-2 (parent and self-report profiles) is administered at screening, baseline, and weeks 2, 4, 6, 9, 12, and 13. As the CDI-2 is designed for children 7 to 17 years of age, children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.

The CDI-2 Self-report is a 28-item self-report questionnaire assessing depressive symptoms in children 7 to 17 years of age with basic reading and comprehension skills. In the CDI-2, children are asked to choose 1 of 3 statements that most closely aligns with their feelings in the previous 2 weeks. The questionnaire covers both the major and minor symptoms of depression as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (Sun and Wang 2015).

The CDI-2 Parent is a 17-item questionnaire administered to parents to assess depression-related behaviors observed in their children. In the CDI-2 Parent, parents are asked to rate their child's behaviors in the past 2 weeks on a 4-point Likert scale from "not at all" to "much or most of the time". The questionnaire allows for the division of depressive symptoms into functional problems and emotional problems (Sun and Wang 2015).

A reference sample is provided in Appendix D.

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 the 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 (LSO/Syneos Health) with the completed pregnancy form.

9. STATISTICS

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

9.1. Sample Size and Power Considerations

It is estimated that approximately 58 patients per arm will enable a power of at least 90% to detect a beneficial standardized effect of 63% or more when the TEV-50717 arm is compared to placebo (difference of 6.0 in the change from baseline to week 12 in TTS, assuming a standard deviation of 9.5 in each arm) in a 2-sided type I error rate of 5% after accounting for potential dropouts.

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 this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of IMP. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they were randomized.

9.2.3. Modified Intent-to-Treat Analysis Set

The Modified Intent-to-Treat (mITT) analysis set will include all patients in the ITT population who receive at least 1 dose of IMP and have both a baseline and at least 1 post-baseline YGTSS assessment. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. All primary and secondary analyses will be based on the mITT set.

9.2.4. Per-Protocol Analysis Set

The per-protocol analysis set will include patients who are compliant with study medication (80% to 105%), have a YGTSS assessment at baseline and at week 9 or week 12, who have not taken prohibited concomitant medications as indicated in exclusion criterion, and who have no

[redacted]

9.6. Multiple Comparisons and Multiplicity

The hierarchical testing method will be used to maintain the experiment-wise type I error of 5% level for the primary and key secondary analyses. The primary efficacy endpoint will first be tested at the 5% type I error level. If the p-value of the primary analysis is ≤0.05, the secondary hypotheses will be tested in the order listed for the secondary endpoints (Section 9.5.2) until either an analysis produces a p-value >0.05 or all analyses result in a p-value ≤0.05.

9.7. Safety Endpoints and Analysis

Safety analyses will be performed on the safety analysis set.

9.7.1. Safety Endpoints

Safety endpoints for this study are as follows:

- incidence of adverse events
- observed values and changes from baseline in vital signs
- observed values and change from baseline in the CDI-2 (Parent and Self-report versions)
- observed values in the C-SSRS
- observed values in ECG parameters and shifts from screening for clinically significant abnormal findings
- observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis)

9.7.2. Safety Analysis

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, adverse events determined by the investigator to be related to study treatment, 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.

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

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

10. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, IMP label records, diary data, protocol-required worksheets, and CRFs that are used as the source (see Section 3.12).

The investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the sponsor.

12.4. Declaration of the End of Clinical Study

The end of study is defined as the date of the week 14 visit of the last participant.

For investigational centers located in the European Union, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/EC, Article 10(c); for other countries, national and local regulations will be followed.

12.5. Registration of the Clinical Study

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