**Study Endpoints:**

**Safety Endpoints:**

**The following safety endpoints will be assessed in Part A (Day 1, Titration, and Maintenance):**

- incidence of adverse events
- observed values and changes from day 1 in vital signs
- observed values and changes from day 1 in the Children's Depression Inventory, Second Edition, Parent and Self-Report Profiles (CDI-2)
- observed values in the Children's Columbia-Suicide Severity Rating Scale (C-SSRS)
- observed values in electrocardiogram (ECG) parameters and shifts from parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17) for clinically significant abnormal findings
- observed values and changes from day 1 in clinical laboratory parameters (hematology, serum chemistry, and urinalysis)

**The following safety endpoints will be assessed in Part B (Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal):**

- incidence of adverse events

In addition to routine monitoring of adverse events, clinical laboratory parameters, 12-lead ECGs, and safety scales, an Independent Data Monitoring Committee will monitor safety during the conduct of the study.

**Efficacy Endpoints:**

**The following efficacy endpoints will be assessed in Part A (Day 1, Titration, and Maintenance):**

- change in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) from day 1 to each visit in which the scale is administered
- change in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score from day 1 to each visit in which the scale is administered
- change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from day 1 to each visit in which the scale is administered
- change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS-QOL) activities of daily living (ADL) subscale score from day 1 to each visit in which the scale is administered

**The following efficacy endpoint will be assessed in Part B (Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal):**

- change in the TTS of the YGTSS from week 28 to week 30, with the primary analyses and sensitivity testing done as described in Section 9.5.3.1

| Abbreviation | Term |
|---|---|
| GSS | Global Severity Score |
| HD | Huntington's disease |
| IA | interim analysis |
| IB | Investigator's Brochure |
| ICH | International Conference for Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IEC/IRB | Independent Ethics Committee/Institutional Review Board |
| IMP | investigational medicinal product |
| IND | Investigational New Drug |
| IRT | Interactive Response Technology |
| ITT | intent-to-treat |
| LSO | local safety officer |
| MINI Kid | Mini International Neuropsychiatric Interview For Children and Adolescents (version 6.0) |
| mITT | Modified Intention-to-Treat |
| MTSS | Motor Tic Severity Score |
| NDA | New Drug Application |
| NOAEL | no-observed-adverse-effect level |
| OCD | obsessive-compulsive disorder |
| PND | postnatal day |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| RBC | red blood cell |
| RSI | reference safety information |
| RWITT | Randomized Withdrawal Intent-to-Treat Population |
| RWmITT | Randomized Withdrawal Modified Intent-to-Treat |
| RRWmITT | Responder Randomized Withdrawal Modified Intent-to-Treat |
| RWSAF | Randomized Withdrawal Safety Population |
| SLV | Since Last Visit |
| SOP | Standard Operating Procedure |
| SUSAR | suspected unexpected serious adverse reaction |
| Tbil | total bilirubin |

The following safety endpoint will be assessed in Part B:

- incidence of adverse events

In addition to routine monitoring of adverse events, clinical laboratory parameters, 12-lead ECGs, and safety scales, an Independent Data Monitoring Committee (IDMC) will monitor safety during the conduct of the study.

### 2.3.2. Efficacy Endpoints

The following efficacy endpoints will be assessed in Part A:

- change in the YGTSS TTS from day 1 to each visit in which the scale is administered
- change in the TS-CGI score from day 1 to each visit in which the scale is administered
- change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from day 1 to each visit in which the scale is administered
- change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS-QOL) activities of daily living (ADL) subscale score from day 1 to each visit in which the scale is administered

The following efficacy endpoint will be assessed in Part B:

- change in the TTS of the YGTSS from week 28 to week 30, with the primary analyses and sensitivity testing done as described in Section 9.5.3.1

### 2.3.3. Exploratory Endpoints

The following exploratory endpoints will be assessed in Part A:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]

involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

The assessments and procedures performed during each study visit are detailed in Table 1 and Section 3.13.

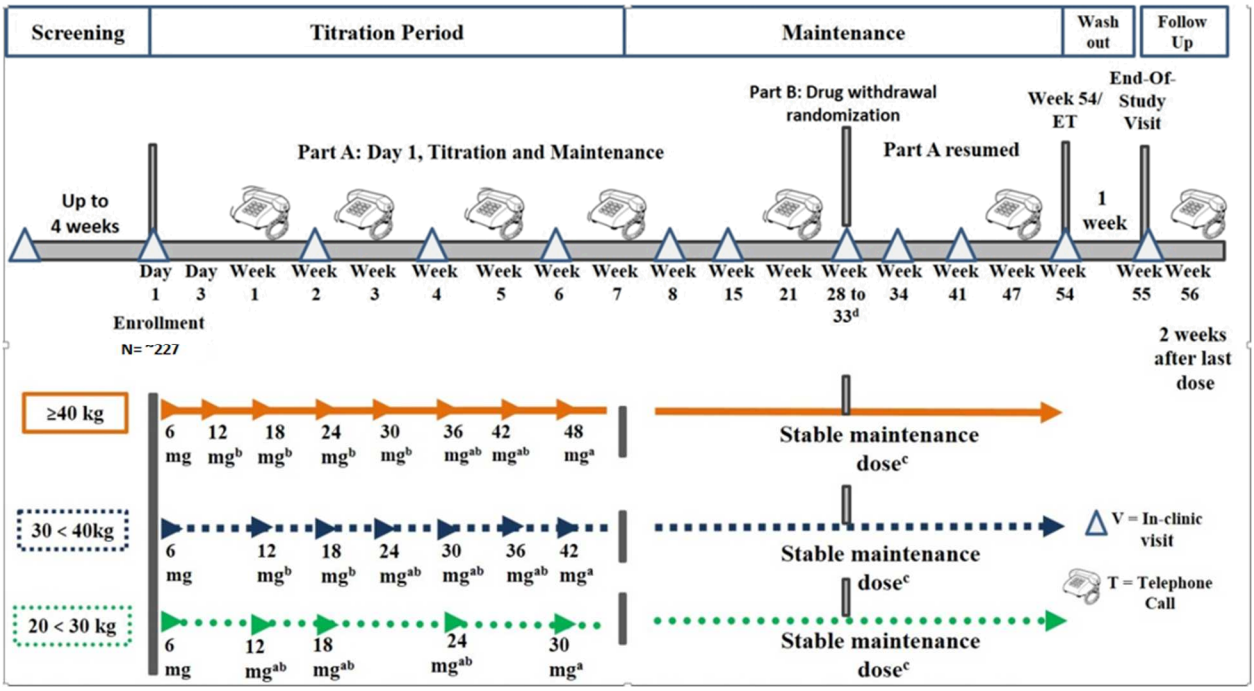
Up to approximately 227 patients are planned to be enrolled (approximately 1 patient is estimated to enroll from the Phase 1b Study SD-809-C-17, up to approximately 99 patients are estimated to enroll from the Phase 2/3 Study TV50717-CNS-30046, and up to approximately 127 patients are estimated to enroll from the Phase 3 Study TV50717-CNS-30060).

When approximately 100 patients have completed the 28-week clinic visit, an interim analysis, including data from day 1 and up to week 28 visit only, will be conducted to provide descriptive, long-term safety and efficacy data to be used in regulatory submissions. To maintain data integrity of Study TV50717-CNS-30047, only a limited number of personnel who do not have contact with the sites will have access to this interim data in preparation for the regulatory filing. As no decisions regarding conduct of the study will be made based on the descriptive interim analysis, no alpha will be spent.

Patients who complete all scheduled visits will have procedures and assessments performed at the final visit (week 54). Patients who withdraw from the study before completing the week 54 evaluation period will have the week 54 procedures and assessments performed at their final visit, and a follow-up telephone contact for safety evaluation 2 weeks after their last dose of IMP.

The study schematic diagram is presented in Figure 1. An additional diagram that details the blinded, randomized drug withdrawal/titration post-drug withdrawal period (Part B of the study) is presented in Figure 2.

**Figure 1: Overall Study Schematic Diagram**



Preliminary efficacy and safety data for TEV-50717 as a treatment for TS have been generated in an open-label, Phase 1b pilot study (SD-809-C-17) in patients. Results of Study SD-809-C-17 support further development of TEV-50717 as a treatment of TS.

Two parent studies, TV50717-CNS-30046 and TV50717-CNS-30060, are underway. They are randomized, double-blind, placebo-controlled studies of the efficacy and safety of TEV-50717 on the tics in patients with TS. This is an open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period in which patients with TS may be eligible to participate after successful completion of any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients who have successfully completed a parent study may be eligible to enroll in this study after they complete a 1-week washout period and the final evaluation in the parent study. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that visit, they can enroll up to 1 week following the week 13 or week 9 visits, respectively. The end of study is defined as the date of the week 56 visit of the last participant.

Inclusion and exclusion criteria have been designed to minimize the risk to patients while maintaining a consistent level of TS symptoms to allow detection and analysis of a drug effect. Exclusion criteria were designed to exclude patients with concomitant conditions that may increase their risk to drug treatment.

The open-label study design (ie, no placebo or comparator) was selected to allow further evaluation and review long-term safety of TEV-50717 in this patient population. Patients will receive twice daily dosing for up to 54 weeks (those on the 6-mg dose will receive once-daily dosing), with an initial 7-week titration period to allow for optimal dose selection. At the week 28 visit, patients will begin a 2-week blinded, randomized drug withdrawal period. The randomized drug withdrawal period will rigorously assess the long-term maintenance of effect. Patients will be randomized to their current dose of TEV-50717 or placebo for 2 weeks. After completing the 2 weeks, patients will continue their same dose of TEV-50717 in a blinded manner or will be re-titrated (patients receiving placebo only) in a blinded manner for 3 weeks. At week 34, all patients will resume their maintenance dose. This is a classic ABA study design (ie, drug, placebo, drug) that allows for a more rigorous test of the intervention. In the traditional AB design, changes in symptoms (particularly in a long trial) could be attributed to other factors (eg, life changes, societal issues, and regression to the mean); however, an acute change demonstrated only in a placebo group among subjects that have been maintained for several months would reduce the likelihood of any other explanations for changes in symptoms.

## 3.3. Safety Measures and Time Points

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

Part A:

- 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 (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients) and week 54
- neurological examination: screening (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients) and week 54
- vital signs, height, and weight: screening (only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); day 1; and weeks 2, 4, 6, 8, 15, 34, 41, 54, and 55
  - Note: orthostatic blood pressure (BP) and pulse on day 1 and weeks 4, 8, and 54
- MINI Kid: screening (only for patients who completed Study SD-809-C-17)
- Children's C-SSRS:
  - Baseline/screening scale: screening (only for patients who completed Study SD-809-C-17)
  - Since Last Visit (SLV) scale: day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55
- CDI-2 (Parent and Self-Report Profiles): screening and day 1 (ie, only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 34, 41, 54, and 55
- 12-lead ECG: screening (ie, only for patients who completed Study SD-809-C-17); day 1; and weeks 4, 8, and 54
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): screening (ie, only for patients who completed Study SD-809-C-17; data from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 should be used for the remaining patients); day 1; and weeks 8 and 54
- pregnancy testing (beta-human chorionic gonadotropin [β-HCG]): screening (ie, only for patients who completed Study SD-809-C-17); day 1 and weeks 4, 8, 15, 34, and 54 (serum tests at screening and week 54 and urine tests at other visits)
- drug screen: screening (ie, only for patients who completed Study SD-809-C-17)

Part B:

- adverse events and concomitant medications: from the signing of the informed consent/assent, depending on the child's age, as appropriate, form through follow-up, inclusive of all visits and telephone contacts
- physical examination: weeks 28 and 30
- vital signs, height, and weight: weeks 28, 30, and 32
  - Note: orthostatic BP and pulse at week 28
- Children's C-SSRS:

current dose or placebo in order to check for return of symptoms. During the entire 5-week period, patients randomized to TEV-50717 will stay on their established maintenance dose of blinded active IMP. Patients who receive placebo during the randomized drug withdrawal period will undergo blinded re-titration post-drug withdrawal. All patients will return to open-label dosing at week 34 (note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients will be known to be on active treatment at the start of week 34).

During the blinded drug withdrawal and re-titration period, patients and investigators will remain blinded to treatment assignment. In addition, the sponsor's and development partner's clinical personnel and all vendors (with the exception of the Interactive Response Technology [IRT] vendor and the IMP packaging vendor) involved in the study will be blinded to the IMP identity until the database has been locked for analysis and the treatment assignments are revealed.

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

The randomized treatment and medication allocation will be assigned to the relevant treatment groups through a qualified service provider (ie, via IRT). The management of the IRT system will be done by a qualified service provider under the oversight of Nuvelution TS Pharma, Inc. (referred to hereafter as Nuvelution TS Pharma).

The staff member at the investigational center who will dispense the IMP will not know the treatment given to each patient during the blinded drug withdrawal and re-titration period.

## 3.6. Maintenance of Randomization and Blinding

### 3.6.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location within Syneos Health. 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 and unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).

### 3.6.2. Blinding and Unblinding

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. The patient's randomized treatment will be made available to the investigator(s) via the IRT system. If possible, the medical monitor should be notified of the event before breaking of the code. If this is not possible, the medical monitor should be notified immediately afterward, and the patient's randomized treatment should not be communicated to the medical monitor. Breaking of the randomization code can always be performed by the investigational center without prior approval by the medical monitor.

When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded on the case report form (CRF). However, if a patient is unblinded by mistake, the

**Table 1: Study Procedures and Assessments**

| | | | Part A | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening[a] | | | Titration | | | | | | | Maintenance | | |
| **Study week**[b] | Parent study | | Day 1[c] | 1 (Day 7) | 2 (Day 14) | 3 (Day 21) | 4 (Day 28) | 5 (Day 35) | 6 (Day 42) | 7 (Day 49) | 8 (Day 56) | 15 (Day 105) | 21 (Day 147) |
| | C-17 | 046 or 060 | | | | | | | | | | | |
| **Visit window (days)** | **<31 days** | **<31 days** | **0** | **±3 days** | | | | | | | | | |
| In-clinic visit | X[d] | | X | | X | | X | | X | | X | X | |
| Telephone contact | | | | X | | X | | X | | X | | | X |
| Evaluate/Adjust IMP | | | | X[e] | X | X[e] | X | X[e] | X | X | | | X |
| Informed consent/assent | X | X[f] | | | | | | | | | | | |
| Eligibility criteria | X | | X | | | | | | | | | | |
| Medical history and psychiatric history | X | [g] | | | | | | | | | | | |
| Demographics | X | [g] | | | | | | | | | | | |
| Vital signs and weight[h] | X | | X[i] | | X | | X[i] | | X | | X[i] | X | |
| Physical examination | X | [j] | | | | | | | | | | | |
| Neurological examination | X | [j] | | | | | | | | | | | |
| Height | X | [j] | X | | X | | X | | X | | X | X | |
| 12-lead ECG[k] | X | | X | | | | X | | | | X | | |
| Chemistry/Hematology/Urinalysis | X | [j] | X[j,l] | | | | | | | | X | | |
| Urine drug screen | X | | | | | | | | | | | | |
| CYP2D6 genotype | [m] | [m] | | | | | | | | | | | |
| β-HCG test[n] | X | | X | | | | X | | | | X | X | |
| MINI Kid[o, p] | X | [g] | | | | | | | | | | | |
| CDI-2 (Parent and Self-Report)[q] | X | | X[r] | | X | | X | | | | X | X | |
| Children's C-SSRS (Baseline/Screen)[p] | X | | | | | | | | | | | | |
| Children's C-SSRS (Since Last Visit) [p] | | | X[r] | | X | | X | | | | X | X | |

| | | | Part A | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening[a] | | | Titration | | | | | | | Maintenance | | |
| **Study week**[b] | Parent study | | Day 1[c] | 1 (Day 7) | 2 (Day 14) | 3 (Day 21) | 4 (Day 28) | 5 (Day 35) | 6 (Day 42) | 7 (Day 49) | 8 (Day 56) | 15 (Day 105) | 21 (Day 147) |
| | C-17 | 046 or 060 | | | | | | | | | | | |
| **Visit window (days)** | **<31 days** | **<31 days** | **0** | **±3 days** | | | | | | | | | |
| YGTSS[s, t] | X | | X[r] | | X[u] | | X | | | | X[u] | X[u] | |
| TS-CGI[t] | | | X[r] | | | | X | | | | X | X | |
| TS-PGII[t] | | | X[r] | | | | X | | | | X | X | |
| [redacted][t] | | | X[r] | | | | X | | | | X | X | |
| [redacted] | | | X[r] | | | | X | | | | X | X | |
| [redacted][p] | | | X[r, v] | | | | | | X[w] | | | | |
| C&A-GTS-QOL (including VAS)[p] | | | X | | | | | | X | | | | |
| Contact IRT and dispense IMP and patient diary | | | X[x] | | X[x] | | X[x] | | X[x] | | X[y] | X[y] | |
| Collect IMP | | | | | X | | X | | X | | X | X | |
| Assess IMP accountability/compliance/supply | | | | X[z] | X | X[z] | X | X[z] | X | X[z] | X | X | X[z] |
| Assess adverse events | X | | X[r] | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications[aa] | X | | X[r] | X | X | X | X | X | X | X | X | X | X |

[a] **Full screening visit is required for patients who previously completed Study SD-809-C-17.** This visit is not required for patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060.

[b] Assessment to occur at the end of study week (±3 days).

[c] For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047, and patients will continue to enter dosing times in the diary through completion of Study TV50717-CNS-30047. Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. Study TV50717-CNS-30047 day 1 assessments that are identical to Study TV50717-CNS-30046 week 13 or Study TV50717-CNS-30060 week 9 visit assessments do not need to be repeated.

[d] The screening visit may be conducted over 2 separate visits at the discretion of the investigator.

[e] Dose adjustment will be made by the investigator after telephone contact with the patient and caregiver/adult to evaluate tic reduction and adverse events (Table 2).

[f] For patients enrolled from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, informed consent/assent, depending on the child's age, as appropriate, may be obtained up to 4 weeks in advance.

[g] For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, these data will be obtained from the screening visit of the parent study.

[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.

- perform clinical laboratory tests, including chemical, hematological, and urine analyses
- perform UDS
- perform a urine/serum pregnancy (β-HCG) test (required for all females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires
  - CDI-2, Parent and Self-Report Profiles (Note: Children 6 years of age on day 1 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.)
- if applicable, dispense additional IMP
- collect used and unused IMP bottles
- assess drug accountability/compliance/supply

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

**6.1.3.** [redacted]

**6.1.4.** [redacted]

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

The C&A-GTS-QOL is administered on day 1 and weeks 6, 28, 34, and 54. Children 13 years of age and under must be interviewed in conjunction with the caregiver/adult. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. 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 4 subscales (psychological, physical, obsessional, and cognitive) 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.

**6.1.6.** [redacted]

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; or 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 Investigational Medicinal Product

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:<br>• It does not follow a reasonable temporal sequence from the administration of the IMP.<br>• 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.<br>• It does not follow a known pattern of response to the IMP.<br>• 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:<br>• It follows a reasonable temporal sequence from administration of the IMP.<br>• 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.<br>• 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.<br>• It follows a known pattern of response to the IMP. |

### 7.1.5. Serious Adverse Events

For recording of serious adverse events, the study period is defined for each patient as the time period from signing of the informed consent/assent form 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 (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
- is 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 ALP)

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

#### 7.1.5.2. Expectedness

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

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

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

- 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 Global Patient Safety and Pharmacovigilance 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.

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 competent authorities (and IEC/IRB, as appropriate), other actions may be required, including:

- 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 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 IMP at any time at the discretion of the investigator. If a post-day 1 QTcF value >500 msec or change from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17), as appropriate (see Section 9.7.2) >60 msec is found, the investigator should repeat the ECG assessment twice and compare the average of the 2 pre-treatment QTcF values (ie, the parent study baseline and screening values for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060 or the day 1 and screening values from the current study for patient[s] who completed Study SD-809-C-17) to the average of the 3 post-day 1 QTcF values. The IMP must be stopped for any confirmed post-day 1 QTcF value >500 msec or increase from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS 30060) or day 1 (Study SD-809-C-17) >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.

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 (CPP)/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 the CDI-2.

### 7.2.1. Mini International Neuropsychiatric Interview for Children and Adolescents, (version 6.0)

Select MINI Kid modules are administered at screening (only for patients who completed Study SD-809-C-17). 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 6.0) 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 version assesses past and current suicidal ideations and behaviors to determine suicide risk and is administered at screening. The C-SSRS children's SLV scale is administered on day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55. 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 administered through 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, patients 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 monitor, the consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.

#### 9.5.3. Planned Method of Analysis

The ITT analysis set (see Section 9.2.1) will be used for all efficacy analyses in Part A. Summaries will be presented for all patients.

##### 9.5.3.1. Efficacy Analysis for the Randomized Drug Withdrawal Period

For the randomized drug withdrawal portion of the study, an analysis of covariance model will be used as the primary analysis model with the change from randomized-withdrawal week 28 to week 30 in YGTSS TTS as the dependent variable, and treatment group, randomized-withdrawal week 28 TTS, and age group at baseline as covariates. The least squares mean of the change in TTS from week 28 to week 30 will be compared (the active treatment arm and placebo arm) using a 2-sided test at the alpha=0.05 level of significance.

The primary analysis will be in the RRWmITT population (see Section 9.2.6). In addition, sensitivity testing will be done using the same model in the RWmITT population and in a subpopulation of the RRWmITT who had a ≥35% reduction in the TTS from baseline in the parent protocol to week 28.

### 9.6. Multiple Comparisons and Multiplicity

This does not apply to this study.

### 9.7. Safety Endpoints and Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.2) for the open-label study and the RWSAF set for the randomized drug withdrawal portion.

#### 9.7.1. Safety Endpoints

The following safety endpoints will be assessed in Part A (Day 1, Titration, and Maintenance):

- incidence of adverse events
- observed values and changes from day 1 in vital signs
- observed values and changes from day 1 in the CDI-2 (Parent and Self-Report Profiles)
- observed values in the C-SSRS
- observed values in electrocardiogram (ECG) parameters and shifts from parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17) for clinically significant abnormal findings

- observed values and changes from day 1in clinical laboratory parameters (hematology, serum chemistry, and urinalysis)

The following safety endpoint will be assessed in Part B (Blinded, Randomized Drug Withdrawal Period and Titration Post-Drug Withdrawal Period):

- incidence of adverse events

In addition to routine monitoring of adverse events, clinical laboratory parameters, 12-lead ECGs, and safety scales, an IDMC will monitor safety during the conduct of the study.

### 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 (overall and by severity), adverse events determined by the investigator to be related to 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. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively.

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 ECG parameters will be summarized, and counts and percentages of abnormal findings will be presented. Changes from parent study baseline (for patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or from day 1 (for patient[s] rolling over from Study SD-809-C-17) in ECG parameters will be summarized descriptively. In addition, the number and percentage of patients with on-treatment QTcF values >450, >480, or >500 msec and change from baseline (Study TV50717-CNS-30046 or Study TV50717-CNS-30060) or day 1 (Study SD-809-C-17) >30 or >60 msec will be presented.

Observed values in the C-SSRS and observed values and changes from baseline in the CDI-2 (Parent and Self-Report Profiles) will be presented for all patients.

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.

## 9.8. Tolerability Variables and Analysis

Tolerability was not specifically defined.

## 9.9. Planned Interim Analysis

When approximately 100 patients have completed the 28-week clinic visit, an interim analysis, including data from day 1 and up to week 28 visit only, will be conducted to provide descriptive, long-term safety and efficacy data to be used in regulatory submissions. To maintain data integrity of Study TV50717-CNS-30047, only a limited number of personnel who do not have contact with the sites will have access to this interim data in preparation for the regulatory filing.

# 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. Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult.

For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, informed consent/assent, as appropriate, may be obtained prior to the day 1 visit, up to 4 weeks in advance of open-label study participation.

## 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.

**Exploratory Endpoints:**

**The following exploratory endpoints will be assessed in Part A (Day 1, Titration, and Maintenance):**

[redacted]

**General Design and Methodology:**

This is an open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration period in which patients with tics associated with TS may be eligible to participate after successful completion of any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that visit, they can enroll up to 1 week following the week 13 or week 9 visits, respectively. The end of study is defined as the date of the week 56 visit of the last participant.

Patients who have successfully completed a parent study may be eligible to enroll in this study after they complete a 1-week washout period and the final evaluation at week 13 (TV50717-CNS-30046) or week 9 (TV50717-CNS-30060) in the parent study.

Site-administered scales include the YGTSS, [redacted], Mini International Neuropsychiatric Interview For Children and Adolescents (MINI Kid, version 6.0), and the C-SSRS; and self-administered scales include the TS-PGII, [redacted], [redacted], CDI-2, and C&A-GTS-QOL. For the YGTSS, input from the caregiver/adult is required. For [redacted] TS-PGII [redacted], input from the caregiver/adult is permitted. For all other scales, for

| Abbreviation | Term |
|---|---|
| TD | tardive dyskinesia |
| SD-809/TEV-50717 | deutetrabenazine |
| 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 |
| UDS | urine drug screen |
| ULN | upper limit of the normal range |
| USA | United States of America |
| VMAT2 | vesicular monoamine transporter 2 |
| VTSS | Vocal Tic Severity Score |
| WBC | white blood cell |
| YGTSS | Yale Global Tic Severity Scale |

# 3. STUDY DESIGN

## 3.1. General Design and Study Schematic Diagram

This is a 56-week, open-label, single-arm study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration period to evaluate the safety of TEV-50717 in children and adolescents with tics associated with TS after they have successfully completed any of the parent studies (SD-809-C-17 [Phase 1b], TV50717-CNS-30046 [Phase 2/3], or TV50717-CNS-30060 [Phase 3]). Patients rolling over from Study SD-809-C-17 will need to undergo all day 1 assessments. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, the week 13 visit (Study TV50717-CNS-30046) or the week 9 visit (Study TV50717-CNS-30060) will be the day 1 visit for Study TV50717-CNS-30047. If the patient does not wish to enroll in Study TV50717-CNS-30047 at that visit, they can enroll up to 1 week following the week 13 or week 9 visits, respectively.

For patients rolling over from Study SD-809-C-17, this study will consist of a 4-week screening period (up to 31 days) and up to 54 weeks of treatment. All participating patients are expected to participate in this study for its entire duration, which is a minimum of 56 weeks. Patients will have a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of IMP). The end of study is defined as the date of the week 56 visit of the last participant.

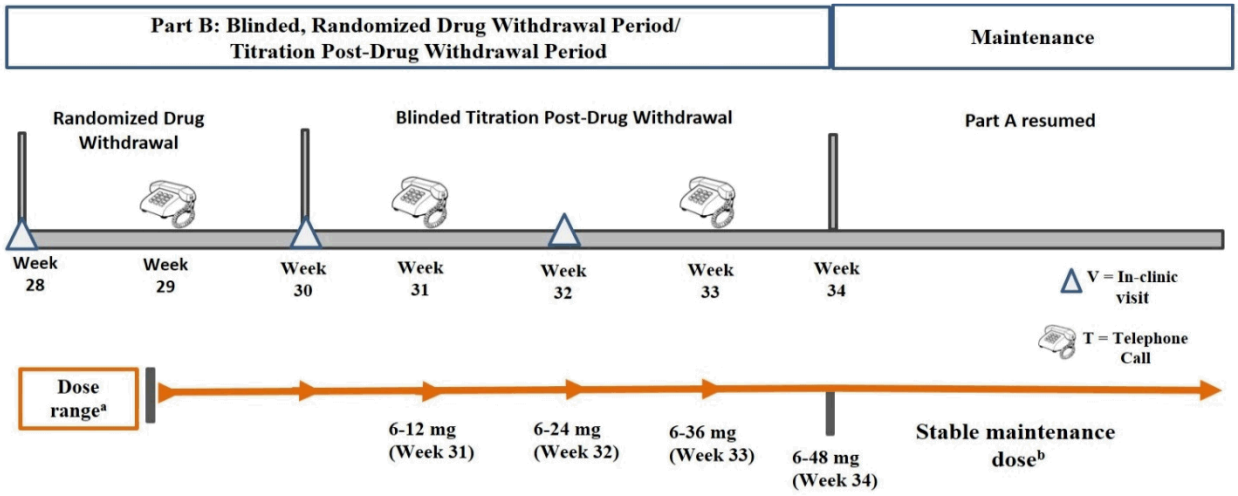
Informed consent/assent, depending on the child's age, as appropriate, will be obtained before any study procedures are performed. For patients rolling over from Study TV50717-CNS-30046 or Study TV50717-CNS-30060, informed consent/assent, as appropriate, may be obtained prior to the day 1 visit, up to 4 weeks in advance of open-label study participation. Any patient that turns 18 years of age during the course of Study TV50717-CNS-30047 will need to be re-consented as an adult.

Patients who have successfully completed any of the parent studies may be eligible to enroll in the current study after they complete a 1-week washout period and the final evaluation (week 13 in Study TV50717-CNS-30046 or week 9 in Study TV50717-CNS-30060) in the parent study. To reduce patient burden, after obtaining informed consent/assent, depending on the child's age, as appropriate, some data collected in Study TV50717-CNS-30046 or Study TV50717-CNS-30060 will be used to provide corresponding day 1 data in the current open-label study (see Table 1).

All screening procedures will be performed for patients rolling over from Study SD-809-C-17, as they will have been off IMP for several months at the time of enrollment into the current study. Site-administered scales include the YGTSS, [redacted], Mini International Neuropsychiatric Interview for Children and Adolescents (MINI Kid, version 6.0), and the C-SSRS and self-administered scales include the TS-PGII, [redacted], CDI-2, and C&A-GTS-QOL. For the YGTSS, input from the caregiver/adult is required. For [redacted] the TS-PGII [redacted], input from the caregiver/adult is permitted. For all other scales, children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or as defined by the scale. For children over 13 years of age, caregiver/adult

[a] Maximum total daily dose for patients ≥40 kg is 48 mg/day (24 mg bid), 30 to <40 kg is 42 mg/day (21 mg bid), and 20 to <30 kg is 30 mg/day (15 mg bid). For those considered CYP2D6 impaired, maximum daily dose for patients ≥40 kg is 36 mg/day, 30 to <40 kg is 24 mg/day, and 20 to <30 kg is 18 mg/day (Table 2).
[b] If a stable dose is reached before the indicated time, the patient should continue taking that dose for the remainder of the titration period and throughout the maintenance therapy dosing.
[c] Dose adjustments may be made, as necessary, except for Part B.
[d] See Figure 2.
Note: Screening visit is required only for patients rolling over from Study SD-809-C-17.
bid=twice daily; CYP=cytochrome P450; ET=early termination visit.

**Figure 2: Study Schematic Diagram (Part B)**




[a] Ranges account for different dosing schedules for patients based on their previously established maintenance dose in Part A. Re-titration only applies to patients who were randomized to placebo during the withdrawal period.
[b] Dose adjustments may be made, as necessary.

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

### 3.1.1. Screening Period (up to 31 days)

For patients from Study SD-809-C-17:

Screening period (up to 31 days): All screening procedures will be performed for patients rolling over from Study SD-809-C-17, as they will have been off IMP for several months at the time of enrollment into this study (TV50717-CNS-30047).

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, assessment of vital signs, laboratory testing, and 12-lead ECG, along with rating scales to assess comorbid TS symptoms and behavioral status.

  - SLV version: weeks 28 and 30
- CDI-2 (Parent and Self-report Profiles): weeks 28 and 30
- 12-lead ECG: week 28
- clinical laboratory tests (serum chemistry, hematology, and urinalysis): week 28
- pregnancy testing: week 28

## 3.4. Efficacy Measures and Time Points

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

### 3.4.1. Efficacy Measures and Time Points

**Part A and Part B:**

- YGTSS: Screening (only for patients who completed Study SD-809-C-17); day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060); and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55
- TS-CGI: Day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55
- TS-PGII: Day 1 (ie, week 13 data from Study TV50717-CNS-30046 or week 9 data from Study TV50717-CNS-30060) and weeks 4, 8, 15, 28, 34, 41, 54, and 55
- C&A-GTS-QOL (ADL subscale): Day 1 and weeks 6, 28, 34, and 54

### 3.4.2. Exploratory Measures and Time Points

**Part A and Part B:**

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

## 3.5. Randomization and Blinding

This is an open-label study that includes a 2-week, double-blind, placebo-controlled, randomized drug withdrawal period followed by a 3-week blinded re-titration period. At the start of the randomized drug withdrawal period (end of week 28), the patients will be randomized 2:1 to 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. Assignment of IMP should not be recorded in any study documents or source document.

In studies with blinding, 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 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.

## 3.7. Independent Data Monitoring Committee

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

The 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 and development partner may be present, and information is provided and discussed in a blinded manner. 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. Investigational Medicinal Product and Placebo Used in the Study

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.

During the open-label period, TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. Each dose strength will have a marking of SD 6, SD 9, and SD 12 corresponding

[j] For patients rolling over from Study TV50717-CNS-30046, these data will be obtained from the week 12 visit of the parent study. For patients rolling over from Study TV50717-CNS-30060, these data will be obtained from the week 8 visit of the parent study.
[k] All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.
[l] For patients with clinically significant laboratory abnormalities at week 12 in Study TV50717-CNS-30046, the week 13 value will serve as the day 1 in this study. For patients with clinically significant laboratory abnormalities at week 8 in Study TV50717-CNS-30060, the week 9 value will serve as the day 1 in this study. Rollover for such patients must be approved by the medical monitor and may be delayed.
[m] Genotype data will be obtained from the relevant parent study. For the patients rolling over from Study SD-809-C-17, these data will come from the CSR and will be communicated to the relevant investigator.
[n] For females who are postmenarchal or ≥12 years of age, a urine test will be administered on day 1 and weeks 4, 8, 15, 28, and 34. A serum test will be administered at screening, week 54, and if clinically indicated.
[o] MINI Kid modules to be used are as follows: 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).
[p] 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.
[q] Children 6 years of age at day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.
[r] For patients rolling over from Study TV50717-CNS-30046, these data will be obtained from the week 13 visit of the parent study. For patients rolling over from Study TV50717-CNS-30060, these data will be obtained from the week 9 visit of the parent study.
[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] A complete assessment will be performed for patients who completed Study SD-809-C-17. For patients who completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060, only perform the Severity Ratings of OCD symptoms (Questions 1 through 10); checklist does not need to be performed.
[w] Perform the Severity Ratings of OCD symptoms (Questions 1 through 10) only. Checklist does not need to be performed.
[x] Study drug 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 weight-based dosing titration.
[y] Patients will receive enough doses to cover treatment until the following in-clinic visit.
[z] The site needs to discuss the drug status during the telephone contacts to ensure the patient has adequate tablets, inform the patient if they should titrate (only during the titration period), and remind them to bring completed bottles to the next in-clinic visit.
[aa] 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 medication should be reviewed with the investigator.

ADHD=Attention Deficit Hyperactivity Disorder; β-HCG=beta-human chorionic gonadotropin; BP=blood pressure; CDI-2=Children's Depression Inventory, Second Edition, Parent and Self-Report Profiles; CSR=clinical study report; C-SSRS=Columbia-Suicide Severity Rating Scale; CY-BOCS=Children's Yale-Brown Obsessive-Compulsive Scale; CYP2D6=cytochrome P450 2D6; ECG=electrocardiogram; ET=early termination visit; C&A-GTS-QOL=Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life; IMP=Investigational Medicinal Product; IRT=Interactive Response Technology; MINI Kid=Mini International Neuropsychiatric Interview For Children and Adolescents (version 6.0); TS-CGI=Tourette Syndrome-Clinical Global Impression; OCD=obsessive-compulsive disorder; TS-PGII=Tourette Syndrome-Patient Global Impression of Impact; TS-PGIS=Tourette Syndrome-Patient Global Impression of Severity; U=unscheduled visit; UA=urinalysis; VAS=visual analog scale; YGTSS=Yale Global Tic Severity Scale.

# 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 the sponsor/development partner (see Section 11.1.2).

## 4.1. Patient Inclusion Criteria

Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 have already met the criteria below.

In addition, patients who have completed Study SD-809-C-17 may be included in the study if, during screening, they meet all of the following criteria:

a. Patient is younger than 18 years of age on day 1.
b. Patient weighs at least 44 pounds (20 kg) on day 1.
c. Patient is able to swallow IMP whole.
d. Patient and caregiver/adult are willing to adhere to IMP regimen and comply with all study procedures.
e. Patient is in good general health, as indicated by medical and psychiatric history as well as physical and neurological examination.
f. 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.
g. Patient and caregiver/adult provide written informed consent/assent, depending on the child's age, as appropriate, according to local regulations.
h. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative β-HCG test on day 1 or are sterile. Definitions of sterile are given in Appendix L.
i. 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 last dose of IMP. Further details are included in Appendix L.

## 4.2. Patient Exclusion Criteria

Patients who have completed Study TV50717-CNS-30046 or Study TV50717-CNS-30060 have already been confirmed to not meet any of the below criteria.

In addition, patients who have completed Study SD-809-C-17 will not be enrolled if, during screening, they meet any of the following criteria:

a. Patient is 18 years of age or older.
b. Patient has a neurologic disorder other than TS that could obscure the evaluation of tics.
c. The patient's predominant movement disorder is stereotypy (coordinated movements that repeat continually and identically) associated with autism spectrum disorder.
d. Patient has a confirmed diagnosis of bipolar disorder, schizophrenia, or another psychotic disorder.

[redacted]

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 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 Global Patient Safety and Pharmacovigilance.

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

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, Parent and Self-Report Profiles

CDI-2 (Parent and Self-Report Profiles) is administered at screening and day 1 (only for patients who completed Study SD-809-C-17) and weeks 2, 4, 8, 15, 28, 30, 34, 41, 54, and 55. As the CDI-2 is designed for children 7 to 17 years of age, children 6 years of age on day 1 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 physician 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.

As no decisions regarding conduct of the study will be made based on the descriptive interim analysis, no alpha will be spent.

## 9.10. Reporting Deviations from the Statistical Plan

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

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and 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.

## 12.4. Declaration of the End of Clinical Study

The end of study is defined as the date of the week 56 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.