# Statistical Analysis Plan

An Open-Label, Long-Term Safety Study Including a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

Study Number TV50717-CNS-30047

NCT03567291

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# Statistical Analysis Plan for Interventional Studies

**Sponsor Name:** Teva Branded Pharmaceutical Products R&D, Inc.
Nuvelution TS Pharma, INC.

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**Protocol Title:** An Open-Label, Long-Term Safety Study Including a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

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## Approvals

I confirm that I have reviewed this document and agree with the content.

| Approvals | | |
|---|---|---|
| **Syneos Health Approval** | | |
| [redacted] Principal Biostatistician<br>Lead Biostatistician | [redacted] Signature | 29-Oct-2019<br>Date (DD-Mmm-YYYY) |
| [redacted], Director, Biostatistics<br>Senior Reviewing Biostatistician | [redacted] Signature | 29-Oct-2019<br>Date (DD-Mmm-YYYY) |
| **Teva Branded Pharmaceutical Products R&D, Inc. / Nuvelution TS Pharma, INC Approval** | | |
| [redacted]<br>Assoc. Director, Global Statistics, Teva<br>Sponsor Contact | [redacted] Signature | 29-Oct-2019<br>Date (DD-Mmm-YYYY) |
| [redacted]<br>Senior Vice President, Nuvelution<br>Sponsor Contact | [redacted] Signature | **29-oct-2019**<br>Date (DD-Mmm-YYYY) |

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# 1. Glossary of Abbreviations

| Abbreviation | Description |
|---|---|
| ADHD | Attention Deficit Hyperactivity Disorder |
| ADL | Activities of daily living |
| AE | Adverse Event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ANCOVA | Analysis of Covariance |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BDRM | Blinded Data Review Meeting |
| β-HCG | beta human chorionic gonadotropin |
| BP | Blood Pressure |
| BMI | Body Mass index |
| CDI-2 | Children's Depression Inventory, Second Edition |
| CI | Confidence Interval |
| CMH | Cochran-Mantel-Haenszel |
| CRF | Case Report Form |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CY-BOCS | Children's Yale-Brown Obsessive-Compulsive Scale |
| CYP | Cytochrome P450 |
| CYP2D6 | Cytochrome P450 2D6 |
| ECG | Electrocardiogram |
| GCP | Good Clinical Practice |
| GSS | Global Severity Score |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IMP | Investigational Medicinal Product |

| Abbreviation | Description |
|---|---|
| IRT | Interactive Response Technology |
| ITT | Intent-to-Treat |
| LDH | Lactate dehydrogenase |
| LS | Least squares |
| MAR | Missing at Random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | Minimum |
| MINI Kid | Mini International Neuropsychiatric Interview For Children and Adolescents |
| mITT | Modified Intent-to-Treat |
| MNAR | Missing Not at Random |
| MTSS | Motor Tic Severity Score |
| N/A | Not Applicable |
| OCD | obsessive-compulsive disorder |
| PR | Time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram |
| PT | Preferred Term |
| QRS | Graphical deflections corresponding to ventricular depolarization in a typical electrocardiogram |
| RBC | Red Blood Cell |
| RR | Time between the start of one R wave and the start of the next R wave in the ECG |
| RRWmITT | Responder Randomized Withdrawal mITT |
| RWITT | Randomized Withdrawal ITT |
| RWmITT | Randomized Withdrawal Modified Intent-to-Treat |
| RWSAF | Randomized Withdrawal Safety |
| QC | Quality Control |
| QTc | Corrected QT Interval |
| QTcF | Fridericia's corrected QT interval |
| SAE | Serious Adverse Event |

| Abbreviation | Description |
|---|---|
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SE | Standard Error |
| SI | Standard International System of Units |
| SLV | Since last visit |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment Emergent Adverse Event |
| TS | Tourette syndrome |
| TS-CGI | Tourette Syndrome-Clinical Global Impression |
| TS-PGII | Tourette Syndrome-Patient Global Impression of Impact |
| TS-PGIS | Tourette Syndrome-Patient Global Impression of Severity |
| TTS | Total Tic Score |
| TLF | Table, Listing and Figure |
| VAS | Visual Analog Scale |
| VTSS | Vocal Tic Severity Score |
| WBC | White Blood Cell |
| WHO | World Health Organization |
| YGTSS | Yale Global Tic Severity Scale |

# 2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

## 2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

Nuvelution will perform review of all tables, figures and listings before the finalization.

## 2.2. Timings of Analyses

Study includes 3 parts: Part I (open-label, first 28 weeks after enrollment), Part II (double-blind, Week 29 and Week 30) and Part III (3 weeks of blinded titration, followed by 21 weeks open-label) (See Section 3.3).

Two analyses are planned:

1. Interim analysis (IA) done after approximately 100 patients complete Part I. Only Part I results will be included; This interim analysis is being done to provide long term safety and efficacy data for the regulatory filings.
2. Final analysis will be completed when the last patient entered into 047 has completed Week 56 or withdrawal from the study; This analysis will include all 3 parts of the study.

No data will be unblinded until data base lock for all patients at Week 56. The main part of this SAP will cover full study statistical report. Analyses that will be included with the IA will be discussed in Section 10.

An independent Data Monitoring Committee (IDMC) will review descriptive summaries of accumulating safety and patient disposition at a frequency recommended by the IDMC. Further description of the IDMC analyses can be found in the IDMC charter Version 1.0 dated 01 Feb 2018.

# 3. Study Objectives

## 3.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of long-term therapy with TEV-50717.

## 3.2. Secondary Objectives

- To evaluate the efficacy of long-term therapy with TEV-50717 in reducing the severity of Tourette syndrome (TS) tics;
- To confirm long-term maintenance of effect by means of a double-blind, placebo-controlled, randomized drug withdrawal period after 28 weeks of open-label treatment.

## 3.3. Brief Description

This study has 3 sequential phases. The first phase (Part I) (Day 1 to the end of Week 28) is open-label and single arm in which all patients receive TV-50717 and undergo a titration period followed by a maintenance period. In the second phase (Part II) (the start of Weeks 29 through the end of Week 30), patients are randomized (2:1) to either continue their current dose of TEV-50717 or placebo for a 2-week period. In the final open-label phase (Part III), (the beginning of Weeks 31 to the end of Week 56), all patients will receive TV-50717 followed by a 2 week safety follow up period. The study schematic diagram is presented in Table 1.

**Table 1: Overall Study Schematic Diagram**

| Screening [a] | Part I | | Part II | Part III | | |
|---|---|---|---|---|---|---|
| | Titration | Maintenance | Randomized drug withdrawal | Maintenance or titration post-drug withdrawal | Maintenance | Follow-up |
| <31 days | Day 1-Week 7 | Week 8-Week 28 | Week 29-Week 30 | Week 31 - Week 33 | Week 34 - Week 54 | Week 55 – Week 56 |
| - | OL | OL | B | B | OL | - |

OL = Open-Label; B = Blinded.

a. Screening visit is not required and assessments will be pulled from parent studies.

Patients successfully completing any of the parent studies (TV50717-CNS-30046 [Phase 2/3] or TV50717-CNS-30060 [Phase 3], termed “parent studies”, may be eligible to participate. 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.

The protocol allows patients that completed study SD-809-C-17 [Phase 1b] to enroll in this study, however at the time of writing this SAP this is considered highly unlikely. Therefore, the

current SAP does not discuss this scenario. In case that any patient from SD-809-C-17 will enroll in the current study, a SAP addendum will be written to describe how screening and baseline data for patients that completed study SD-809-C-17 as the parent study will be handled.

## 3.4. Patients Selection

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

### 3.4.1. Inclusion Criteria

Refer to protocol section 4.1 for inclusion criteria.

### 3.4.2. Exclusion Criteria

Refer to protocol section 4.2 for inclusion criteria.

## 3.5. Determination of Sample Size

This study has 3 key objectives: to assess the long term safety and tolerability of TEV-50717, to evaluate the efficacy of long-term therapy with TEV-50717 in reducing the severity of Tourette syndrome (TS) tics, and to confirm the long-term maintenance of effect by means of a double-blind, placebo-controlled, randomized, 2-week drug withdrawal period after 28 weeks of open-label treatment. The expected number of patients who are anticipated to enroll in this study are based on the patient's dispositions from the parent study (Table 2).

**Table 2: Planned and Actual Sample Size from Parent Study**

| Study | TV-50717-CNS-30046 | TV-50717-CNS-30060 | Total |
|---|---|---|---|
| Planned (Actual*) Number of Patients Randomized | 116 (109) | 150 (117) | |
| Planned Drop-out Rate in Parent Study (Actual* number withdrawal) | 8% (12) | 8% (10) | |
| Planned (Actual*) Number of Patients Completed | 107 (91) | 138 (85) | |
| Planned rate of patients that complete parent study | 8% | 8% | |

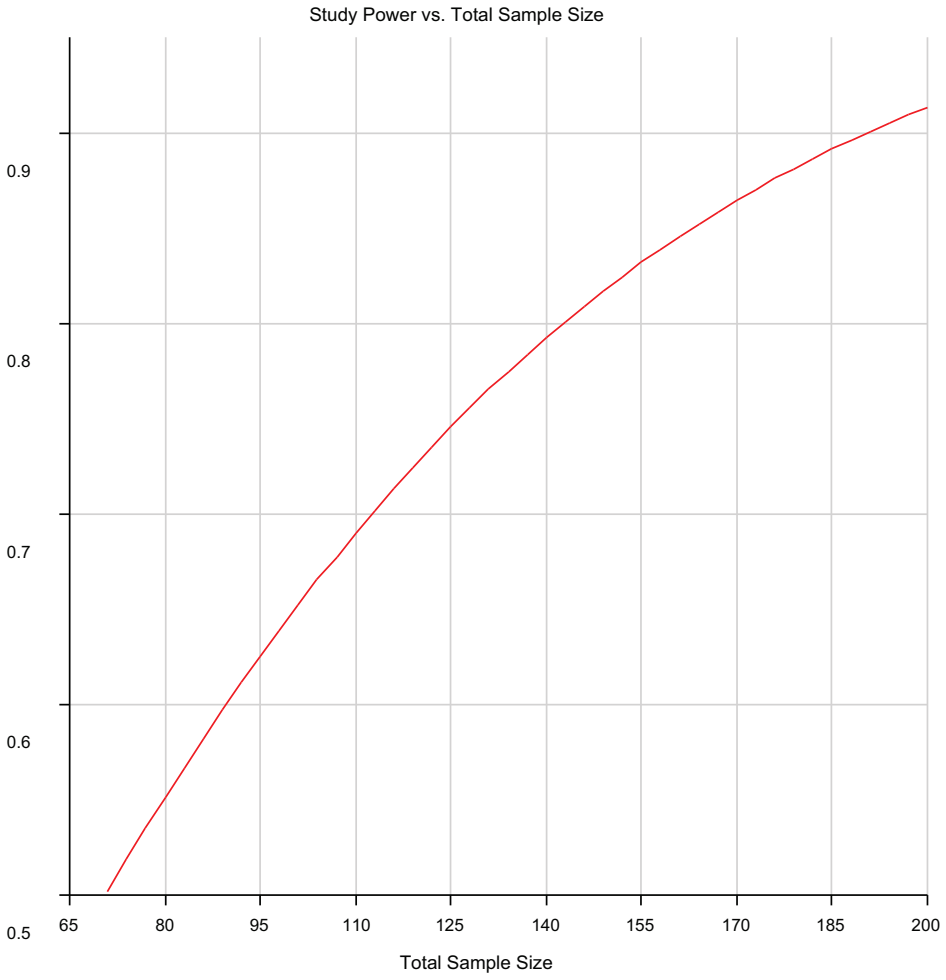
| | | | |
|---|---|---|---|
| and do not enroll in this study | | | |
| Planned (Actual*) Number of Patients enroll into this study | 99 (79) | 127 (78) | 226 (157) |

** All actual numbers as of the date of 09Aug2019. As the parent studies are ongoing the actual number of subjects enrolled in TV-50717-30047 may differ from the numbers shown in this table.*

For the randomized drug withdrawal period, the potential power by sample size is presented in Figure 1. The study power is computed under the specification below:

- The difference between TEV-50717-treated and placebo-treated patients assuming a difference in the Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS) of 4.5;
- Equal standard deviation of 9.0;
- Type 1 error rate of 5%;
- Randomization ratio 2:1 TEV-50717 vs placebo

**Figure 1: Power vs. Sample Size**




Additional factors that can impact the final sample size for the analyses will include:

1. Patients retention rate before Week 28;
2. Proportion of patients who achieve ≥25% reduction in the TTS from baseline in the parent studies to week 28.
3. Additional number of subjects who do not complete the parent studies or do not consent to enroll in this study.

The power to detect the assumed difference will be 90% if at least 190 patients are included in the analysis and it drops below 50% when the sample size is ≤70 patients.

## 3.6. Treatment Assignment & Blinding

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. During Part I and Part III maintenance period, all patients will be treated with TEV-50717. During Part II, patients will be randomized to either receive TEV-50717 or placebo in the ratio of 2:1.

### 3.6.1. Treatment Assignment

During the blinded drug withdrawal and re-titration period, 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 randomization list and treatment will be assigned to the relevant treatment groups through a qualified service provider, i.e., via Interactive Response Technology (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.

### 3.6.2. Blinding

Patient randomization codes for Part II will be maintained in a secure network storage folder with restricted access within Syneos Health, Biostatistics. 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.

The sponsor's clinical personnel and all vendors (with exception of the Interactive Response Technology [IRT] vendor and the bioanalytical sample analysis vendor) involved in the study will be blinded to the Investigational Medicinal Product (IMP) identity until the database is locked for analysis and the treatment assignment revealed.

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 drug 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. 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). 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 studies with blinding, for an adverse event defined as a suspected unexpected serious

adverse reaction (SUSAR) (i.e., reasonable possibility; see protocol 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.

Syneos Health 3910.00 describes the procedures for planning and conducting unblinded analyses prior to database lock for IDMC. Unblinded data, including randomization codes, type of dispensed kits and all subsequent SDTM, ADaM datasets, and analysis results generated from the unblinding information, will be stored under a pre-specified secure area with restricted access. Access to the unblinded folders can only be requested by a manager level or higher within the associate's department. The secure area for storage of data and results (including any report and its appendices) will be maintained so that it can be accessed only by unblinded personnel. All staff involved in the conduct of the trial shall remain ignorant of the results of all unblinded analyses.

## 3.7. Administration of Study Medication

During the open-label periods (Parts I and Part III open-label maintenance period), TEV-50717 tablets are available in the following dose strengths: 6, 9, and 12 mg. 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.

During the randomized drug withdrawal period (Part II) and re-titration period of Part III, TEV-50717 tablets are available in the following dose strengths: 6, 9, 12, 15, and 18 mg, all of which are identical in size, shape, and color (white). The IMP will be supplied in 20-count bottles. The placebo tablets and packaging will match those for TEV-50717.

Patients who receive TEV-50717 during the randomized drug withdrawal period (Part II) will remain on their maintenance dose of blinded active IMP during Part III of the study, and those assigned to placebo during the randomized drug withdrawal period (Part II) will undergo blinded re-titration from the start of week 31 to the start of week 34 back to their previously established maintenance dose from the end of week 28. Note that, because IMP is dispensed for 2-week periods, patients will use blinded bottles through the end of week 34; however, all patients should be on active treatment at the start of week 31.

IMP will be administered as oral tablets at a starting dose of 6 mg once daily. Titration schemes during part I are based on body weight on day 1 and the maximum daily dose is determined by body weight and cytochrome P450 2D6 (CYP2D6) impairment status on day 1. Titration during Part III is based on the previously established maintenance dose in Part I. Refer to protocol Section 5.1 for additional details.

## 3.8. Study Procedures and Flowchart

Study procedures and assessments with their time points are presented in Table 3.

**Table 3: Study Procedures and Assessments**

| | | Part I | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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-46 or C-60** | | | | | | | | | | | |
| **Visit window (days)** | **<31 days** | **0** | **±3 days** | | | | | | | | | |
| In-clinic visit | | X | | X | | X | | X | | X | X | |
| Telephone contact | | | X | | X | | X | | X | | | X |
| Evaluate/Adjust IMP | | | X[d] | X | X[d] | X | X[d] | X | X | | | X |
| Informed consent/assent | X[e] | | | | | | | | | | | |
| Eligibility criteria | | X | | | | | | | | | | |
| Medical history and psychiatric history | [f] | | | | | | | | | | | |
| Demographics | [f] | | | | | | | | | | | |
| Vital signs and weight[g] | | X[h] | | X | | X[h] | | X | | X[h] | X | |
| Physical examination | [i] | | | | | | | | | | | |
| Neurological examination | [i] | | | | | | | | | | | |
| Height | [i] | X | | X | | X | | X | | X | X | |
| 12-lead ECG[j] | | X | | | | X | | | | X | | |
| Chemistry/Hematology/Urinalysis | [i] | X[i,k] | | | | | | | | X | | |
| Urine drug screen | | | | | | | | | | | | |
| CYP2D6 genotype | [z] | | | | | | | | | | | |
| β-HCG test[l] | | X | | | | X | | | | X | X | |
| MINI Kid[m, n] | [f] | | | | | | | | | | | |
| CDI-2 (Parent and Self-Report)[o] | | X[p] | | X | | X | | | | X | X | |

| | | Part I | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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-46 or C-60** | | | | | | | | | | | |
| **Visit window (days)** | **<31 days** | **0** | **±3 days** | | | | | | | | | |
| Children's C-SSRS (Baseline/Screen)[n] | | | | | | | | | | | | |
| Children's C-SSRS (Since Last Visit)[n] | | X[p] | | X | | X | | | | X | X | |
| YGTSS[q, r] | | X[p] | | X[s] | | X | | | | X[s] | X[s] | |
| TS-CGI[r] | | X[p] | | | | X | | | | X | X | |
| TS-PGII[r] | | X[p] | | | | X | | | | X | X | |
| TS-PGIS[r] | | X[p] | | | | X | | | | X | X | |
| Tic-free Interval[n] | | X[p] | | | | X | | | | X | X | |
| CY-BOCS[n] | | X[p, t] | | | | | | X[u] | | | | |
| C&A-GTS-QOL (including VAS)[n] | | X | | | | | | X | | | | |
| Contact IRT and dispense IMP and patient diary | | X[v] | | X[v] | | X[v] | | X[v] | | X[w] | X[w] | |
| Collect IMP | | | | X | | X | | X | | X | X | |
| Assess IMP accountability/compliance/supply | | | X[x] | X | X[x] | X | X[x] | X | X[x] | X | X | X[x] |
| Assess adverse events | | X[p] | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications[y] | | X[p] | X | X | X | X | X | X | X | X | X | X |

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

[f] 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.
[g] 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).
[h] Orthostatic BP and pulse will be measured after patient is in standing position for at least 3 minutes.
[i] 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.
[j] All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.
[k] 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.
[l] 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.
[m] 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).
[n] 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.
[o] Children 6 years of age at day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.
[p] 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.
[q] Input from the caregiver/adult is required.
[r] The YGTSS, TS-CGI, TS-PGII, and TS-PGIS questionnaires should be performed before any blood draws or ECG assessments.
[s] 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.
[t] 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.
[u] Perform the Severity Ratings of OCD symptoms (Questions 1 through 10) only. Checklist does not need to be performed.
[v] 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.
[w] Patients will receive enough doses to cover treatment until the following in-clinic visit.[z]
[x] 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.
[y] 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.
[z] Genotype data will be obtained from the relevant parent study.

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; 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.

**Table 3: Study Procedures and Assessments (continued)**

| | Part II | | | Part III | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Randomized drug withdrawal | | | Maintenance (resumed) or titration post-drug withdrawal | | | Maintenance | | | | Follow-up | | U |
| **Study week**[a] | 28[b] (Day 196) | 29 (Day 203) | 30 (Day 210) | 31 (Day 217) | 32 (Day 224) | 33 (Day 231) | 34 (Day 238) | 41 (Day 287) | 47 (Day 329) | 54/ET[c] (Day 378) | 55 (Day 385) | 56[d] (Day 392) | |
| **Visit window (days)** | ±3 from week 21 | | | ±3 | | ±3 days | | | | | ±3 from week 54 | | |
| In-clinic visit | X | | X | | X | | X | X | | X | X | | X |
| Telephone contact | | X | | X | | X | | | X | | | X | |
| Evaluate/Adjust IMP | | | X | X | X | X | | | | | | | X |
| Informed consent/assent | | | | | | | | | | | | | |
| Vital signs and weight[e] | X[f] | | X | | X | | X | X | | X[b] | X | | X |
| Physical examination | X | | X | | | | | | | X | | | X[c] |
| Neurological examination | | | | | | | | | | X | | | X[g] |
| Height | X | | X | | X | | X | X | | X | X | | X[g] |
| 12-lead ECG[h] | X | | | | | | | | | X | | | X[g] |
| Chemistry/Hematology/Urinalysis | X | | | | | | | | | X | | | X[g] |
| Urine drug screen | | | | | | | | | | | | | X[g] |
| β-HCG test[i] | X | | | | | | X | | | X | | | X[g] |
| CDI-2 (Parent and Self-Report)[j] | X | | X | | | | X | X | | X | X | | X[g] |
| Children's C-SSRS (Baseline/Screening)[k] | | | | | | | | | | | | | |
| Children's C-SSRS (Since Last Visit)[k] | X | | X | | | | X | X | | X | X | | X[g] |
| YGTSS[l, m] | X | | X | | | | X | X | | X | X[n] | | |
| TS-CGI[m] | X | | | | | | X | X | | X | X | | |

| | Part II | | | Part III | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Randomized drug withdrawal | | | Maintenance (resumed) or titration post-drug withdrawal | | | Maintenance | | | | Follow-up | | U |
| **Study week**[a] | **28**[b] **(Day 196)** | **29 (Day 203)** | **30 (Day 210)** | **31 (Day 217)** | **32 (Day 224)** | **33 (Day 231)** | **34 (Day 238)** | **41 (Day 287)** | **47 (Day 329)** | **54/ET**[c] **(Day 378)** | **55 (Day 385)** | **56**[d] **(Day 392)** | |
| **Visit window (days)** | **±3 from week 21** | | | **±3** | | **±3 days** | | | | | **±3 from week 54** | | |
| TS-PGII[m] | X | | | | | | X | X | | X | X | | |
| TS-PGIS[m] | X | | | | | | X | X | | X | X | | |
| Tic-free Interval[k] | X | | | | | | X | X | | X | X | | |
| CY-BOCS[k] | X | | | | | | X | | | X | X[o] | | |
| C&A-GTS-QOL (including VAS)[k] | X | | | | | | X | | | X | | | |
| Contact IRT and dispense IMP and patient diary | X[p] | | X[p] | | X[p] | | X[q] | X[q] | | | | | X[g, r] |
| Collect IMP | X | | X | | X | | X | X | | X | | | X[g] |
| Assess IMP accountability/compliance/supply | X | X[s] | X | X[s] | X | X[s] | X | X | X[s] | X | | | X[g] |
| Assess adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications[t] | X | X | X | X | X | X | X | X | X | X | X | X | X |

[a] Assessments to occur at end of study week (±3 days).
[b] At the week 28 visit, the patients will be randomized 2:1 to their current dose of TEV-50717 or placebo in order to check for return of symptoms.
[c] 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 54 visit.
[d] This visit is a telephone contact for safety evaluation.
[e] Weight must be measured with shoes and outerwear off. Before pulse and BP are measured, the patient must be in a supine or semi erect/seated position and resting for at least 5 minutes (the same position and arm should be used each time vital signs are measured for a given patient).
[f] Orthostatic BP and pulse will be measured after patient is in standing position for at least 3 minutes.
[g] Assessment to be completed at investigator's discretion.
[h] All ECGs will be performed after at least 5 minutes rest in a supine or semi-supine position.
[i] 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.
[j] Children 6 years of age at day 1 will not complete the Self-Report version; the caregiver/adult will complete the Parent version.

[k] 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.
[l] Input from the caregiver/adult is required.
[m] The YGTSS, TS-CGI, TS-PGIS, and TS-PGII questionnaires should be performed before any blood draws or ECG assessments.
[n] 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.
[o] Perform the Severity Ratings of OCD symptoms (Questions 1 through 10) only. Checklist does not need to be performed.
[p] IMP will be dispensed in the clinic; patients will receive doses for 2 weeks (current dose level and next dose level, when applicable [week 30 and week 32 visits]) to cover the telephone contacts. Because IMP for Part II is dispensed then, the week 28 visit (Day 196) is considered the first day of the randomized withdrawal period (part II), although the patient will begin taking blinded IMP on Day 197. When applicable, the site will determine titration (ie, starting the next dose) for the patient by telephone.
[q] Patients will receive enough doses to cover treatment until the following in-clinic visit.
[r] Contact IRT if IMP assignment or adjustment is required.
[s] 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.
[t] 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; 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. Endpoints

## 4.1. Safety Endpoints

The following safety endpoints will be assessed in Parts I and III:

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

The following safety endpoint will be assessed in Part II:

- The incidence of adverse events;
- The observed values and the changes from Week 28 (randomized withdrawal baseline) in the Children's Depression Inventory, Second Edition, Parent and Self-Report Profiles (CDI-2);
- The observed values in the Children's Columbia-Suicide Severity Rating Scale (C-SSRS);

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.

## 4.2. Efficacy Endpoint

The following key efficacy endpoint will be assessed in Part II:

- The change in the TTS of the YGTSS from week 28 (randomized withdrawal baseline) to week 30 (end of randomized withdrawal).

The following exploratory efficacy endpoints will be assessed in Part II:

- [redacted]
- [redacted]

## 4.3. Exploratory Endpoints

The following exploratory endpoints will be assessed in Parts I and III at the visits in which the data is collected:

- [redacted]
- [redacted]

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

# 5. Analysis Sets

## 5.1. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set will include all enrolled patients into this study, regardless of whether or not a patient took any IMP.

This analysis set will be used in all study population and efficacy analyses for Parts I and III combined.

## 5.2. Safety Analysis Set

The Safety Analysis Set will include all patients who receive at least 1 dose of IMP.

The Safety Analysis Set will be used for all safety analyses. This analysis set will be used in all safety analyses for Parts I and III combined.

## 5.3. Randomized Withdrawal ITT Population

The Randomized Withdrawal ITT (RWITT) Population will include all patients that completed Part I and were randomized to Part II (Note that randomization occurs at the week 28 visit).

## 5.4. Randomized Withdrawal Safety Population

The Randomized Withdrawal Safety (RWSAF) Population will include all patients in the RWITT who are administered any study drug in the randomized withdrawal period.

All summaries of safety measures in Part II will be summarized descriptively in the RWSAF Population. All safety summaries based on the RWSAF will used the actual treatment patient received during the randomized drug withdrawal period.

## 5.5. Randomized Withdrawal Modified Intent-to-Treat Population

The Randomized Withdrawal Modified Intent-to-Treat (RWmITT) Population will include all patients in the RWITT who receive study drug in the randomized withdrawal period and have a YGTSS TTS at both the week 28 visit (randomized withdrawal baseline) and the week 30 visit (end of randomized withdrawal).

This study population will be used for sensitivity efficacy analysis in Part II. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

## 5.6. Responder Randomized Withdrawal Modified Intent-to-Treat Population

The Responder Randomized Withdrawal mITT (RRWmITT) Population will include all patients in the RWmITT that had a ≥25% reduction in the TTS from baseline in the parent study to week 28. This study population will be used in the primary efficacy analysis in Part II. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

## 5.7. Protocol Deviations

Protocol deviation management at Syneos Health is detailed in Processing and Management of Protocol Deviations (3100.W02). For details on the process for defining analysis datasets refer to (Blind) Data

Review and Definition of Analysis Sets SOP (3911). Major protocol deviations will be summarized for Parts I and III combined, and Part II.

# 6. General Aspects for Statistical Analysis

## 6.1. General Methods

Statistical methodology and analyses are in accordance with the principles outlined by the ICH E9 guidelines. All statistical analyses will be conducted using SAS statistical software version 9.4 or above.

Tables, listings and figures (TLFs) will be produced in accordance with the principles outlined by the ICH E3 guidelines.

Data summaries will use descriptive statistics (number of patients [n], mean, standard deviation [SD], standard error [SE], median, minimum, and maximum) for continuous variables, and frequency and percentage of patients for categorical and ordinal variables, unless otherwise specified. For continuous variables, if n<5 then only median, min and max will be presented.

Unless otherwise specified, all statistical tests will be two-tailed using a 0.05 level of significance. All confidence intervals (CIs) will be two sided 95% CIs.

Only visits mapped to scheduled visits will be included in by-visit summaries. All visit assessment data will be included in shift tables and will appear in the patient listings.

In general, endpoints assessed in Parts I and III will be summarized for Parts I and III combined and endpoints assessed in Part II will be summarized separately for Part II.

For assessments conducted at each visit, analyses for Parts I and III combined will include Week 28 assessment, but Week 30 assessment will not be included. Summary for Part II will include Week 28 (the randomized withdrawal baseline) and Week 30.

For analyses performed by time period, the date of Week 28 and Week 30 will be considered as the first and last day of Part II, respectively. Summary for Parts I and III combined will not include period between Week 28 assessment and Week 30 assessment, which will be covered under Part II summary.

## 6.2. Key Definitions

### 6.2.1. Baseline Values

Three baseline values will be defined:

- Parent study baseline: Parent study baseline is defined as the last non-missing measurement on or prior to the first dose of study IMP from the parent study. This baseline is used to define RRWmITT population (Section 5.6), sensitivity analysis for the TTS of the YGTSS from Week 28 to Week 30 (Section 8.2.1), and ECG analysis (Section 9.8).
- Baseline: Baseline is defined as the last non-missing measurement on or prior to the first dose of open-label IMP. In general, the Week 13 values from Study TV50717-CNS-30046 or the Week 9 values from Study TV50717-CNS-30060 will serve as baseline in this study, except for the lab assessments. For the patients rolling over from Study TV50717-CNS-30046, the Week 12 lab values will serve as the baseline in this study, or the Week 13 lab values, if the patient repeated lab assessments at Week 13. Similarly, for the patients rolling over from Study TV50717-CNS-30060, the Week 8 lab values will serve as baseline, or the Week 9 lab values if patients repeated lab assessments at Week 9. Baseline will be used for the efficacy and the safety tables for the Parts I and III combined.

- Randomized withdrawal baseline: For the patients who are randomized in Part II, the randomized withdrawal baseline is defined as the measurement at Week 28. This baseline will be used for all efficacy tables and safety tables during randomized withdrawal period.

### 6.2.2. First Dose Date

There are 3 first dose dates:

- The Part I first dose date will be the date that the first dose of open-label IMP is administered;
- The Part II first dose date will be the date that the first dose of the randomized, double-blind IMP is administered;
- The Part III first dose date will be the date that the first dose of the double-blind titration TEV-50717 is administered.

Dose starting and stopping dates in Parts I and III maintenance period are collected on CRF page per week per pills strength (6 mg, 9 mg, and 12 mg). They are collected per dispensed visit per bottle during Part II and Part III titration period. The Part I first dose date will be derived as the earliest dose starting date obtained from CRF. Part II first dose date will be the earliest dose starting date for any bottles dispensed on the Week 28 visit. Part III first dose date will be the earliest dose starting date for any bottles dispensed on the Week 30 visit.

### 6.2.3. Last Dose Date

There are 3 last dose dates that will be used for the analyses:

- The Part I last dose date will be the date of the last dose of the study IMP before the day after Week 28 visit, or the first dose of double-blind IMP if patient is dosed during randomized withdrawal period;
- The Part II last dose date will be the date of the last dose of double-blind IMP during randomized drug withdrawal period;
- The Part III last dose date will be the date of the last dose of open-label IMP during Part III.

### 6.2.4. Study Day

Study Day is the number of days starting from the first administration of open-label IMP, which is counted as Study Day 1. If the assessment date is after the date of the first dose of open-label IMP, the study day is calculated as date of assessment - date of the first dose of open-label IMP +1. If the assessment date is prior to the date of the first dose of open-label IMP, the study day is calculated as date of assessment - date of the first dose of open-label IMP.

### 6.2.5. Duration of IMP

Duration of Part I IMP (day) = The Part I last dose date – The Part I first dose date + 1;
Duration of Part II IMP (day) = The Part II last dose date – The Part II first dose date + 1;
Duration of Part III IMP (day) = The Part III last dose date – The Part III first dose date + 1;

Duration of Part I, II, and III combined IMP will be determined as:

Duration of Part I, II, and III combined IMP (day) = Duration of Part I IMP (day) + Duration of Part II IMP (day) + Duration of Part III IMP (day).

Duration of Parts I and III combined IMP will be determined as:
Duration of Parts I and III combined IMP (day) = Duration of Part I IMP (day) + Duration of Part III IMP (day).

Determination of duration of IMP for any patient that does not fall into one of the categories above will be determined on a case-by-case basis in the statistical data review meeting.

### 6.2.6. Parts Start and End Dates

For adverse events and concomitant medication, analyses are performed by time period. The following definitions will be used:

- Part I
  - Start Date – the day of the Day 1 visit;
  - End Date - the day of the Week 28 visit, or the day before the Part II first dose date, if patient is dosed during Part II and the Part II first dose date is earlier. If a patient is enrolled but discontinues treatment before the Week 28 visit, Part I is until the last dose of study treatment.
- Part II (The randomized withdrawal period):
  - Start Date - the day after the Week 28 visit, or the Part II first dose date, if it is earlier;
  - End Date the day of the Week 30 visit. If a patient is randomized but discontinues treatment before the Week 30 visit, Part II is until the last dose of study treatment.
- Part III:
  - Start Date - the day after Week 30 visit;
  - End Date - the day of the Week 56 visit. If a patient completed Part II, but discontinues before the Week 56 visit, Part III is until the last dose of study treatment.

### 6.2.7. Periods Start and End Dates

Adverse events will also be summarized by periods below:

- Part I Titration Period
  - Start Date - the Day 1 visit;
  - End Date - the last dose of study treatment during titration period (up to and including Week 8 visit).
- Part I Maintenance Period
  For patients who completed any assessments after Week 8 visit, the start and end dates are:
  - Start Date - the day after Week 8 visit;
  - End Date - the Part I last dose date .
- Part II and III Treatment Period
  For patients who are randomized
  - Start Date - the start date of Part II;
  - End Date - the last dose of study treatment during the study.
- Follow-up Period
  - Start Date - the day after the last dose of study treatment;
  - End Date - the day of the last visit.

Periods are not corresponding to Parts. Events occurred after last dose of study treatment are included with each Parts, but are not included period. Events after the last dose of study treatment will all be summarized with the follow-up period.

#### 6.2.8. Exposure-Adjusted Incidence Rate

Exposure-Adjusted Incidence Rate (EAIR) is calculated as the number of patients with an AE divided by patient-years of treatment. For calculating patient years, patients with an AE contribute with treatment exposure up to the day of their first contributing AE, patients without an AE contribute their entire treatment duration in the Part or Periods event.

### 6.3. Missing Data

In general, only the observed data from the patients will be used in the statistical analyses. No data imputation will be applied for missing values.

### 6.4. Visit Windows

For efficacy and safety by-visit analyses, data collected at post baseline scheduled visits will be included using their scheduled visit and data collected at early termination and unscheduled visits will be included and assigned to a visit window as described below.

Efficacy: Visit Windows for Unscheduled or Early Termination Visit

| Assessment | Study Day Window | Scheduled day | Scheduled Visit/Week |
|---|---|---|---|
| YGTSS | Day 2 - 21 | Day 14 | Week 2 |
| | Day 22 - 42 | Day 28 | Week 4 |
| | Day 43 - 80 | Day 56 | Week 8 |
| | Day 81 - 150 | Day 105 | Week 15 |
| | Day 151 – Date of first dose of double-blind IMP (or Date of randomization, if first dose date is missing) if patient is randomized; Day 151 – Day 203 if patient is not randomized | Day 196 | Week 28/Beginning of Part II |
| | Day after Part II first dose (or Date of randomization, if first dose date is missing) - Week 30 visit date (or Day 224 if subject terminated before Week 30 visit) | Day 210 | Week 30 |
| | Day after Week 30 visit - 262 | Day 238 | Week 34/Part III |
| | Day 263 - 332 | Day 287 | Week 41 |
| | Day 333 - 382 | Day 378 | Week 54 |
| | ≥Day 383 | Day 385 | Week 55 |
| TS-CGI, TS-PGI, Tic-free Interval | Day 2 - 42 | Day 28 | Week 4 |
| | Day 43 - 80 | Day 56 | Week 8 |
| | Day 81 - 150 | Day 105 | Week 15 |
| | Day 151- 217 | Day 196 | Week 28/Beginning of Part II |
| | Day 218 - 262 | Day 238 | Week 34/Part III |
| | Day 263 - 332 | Day 287 | Week 41 |
| | Day 333 - 382 | Day 378 | Week 54 |

| Assessment | Study Day Window | Scheduled day | Scheduled Visit/Week |
|---|---|---|---|
| | ≥Day 383 | Day 385 | Week 55 |
| CY-BOCS | Day 2 - 118 | Day 42 | Week 6 |
| | Day 119- 217 | Day 196 | Week 28/Beginning of Part II |
| | Day 218 - 308 | Day 238 | Week 34/Part III |
| | Day 309 - 382 | Day 378 | Week 54 |
| | ≥Day 383 | Day 385 | Week 55 |
| C&A-GTS-QOL | Day 2 - 118 | Day 42 | Week 6 |
| | Day 119 - 217 | Day 196 | Week 28/Beginning of Part II |
| | Day 218 - 308 | Day 238 | Week 34/Part III |
| | ≥ Day 309 | Day 378 | Week 54 |

Safety: Visit Windows for Unscheduled or Early Termination Visit

| Assessment | Study Day Window | Scheduled day | Scheduled Visit/Week |
|---|---|---|---|
| CDI-2, C SSRS | Day 2 - 21 | Day 14 | Week 2 |
| | Day 22 - 42 | Day 28 | Week 4 |
| | Day 43 - 80 | Day 56 | Week 8 |
| | Day 81 - 150 | Day 105 | Week 15 |
| | Day 151 – Date of first dose of double-blind IMP (or Date of randomization, if first dose date is missing) if patient is randomized; Day 151 – Day 203 if patient is not randomized | Day 196 | Week 28/Beginning of Part II |
| | Day after Part II first dose (or Date of randomization, if first dose date is missing) - Week 30 visit date (or Day 224 if subject terminated before Week 30 visit) | Day 210 | Week 30 |
| | Day 225 - 262 | Day 238 | Week 34/Part III |
| | Day 263 - 332 | Day 287 | Week 41 |
| | Day 333 - 382 | Day 378 | Week 54 |
| | ≥Day 383 | Day 385 | Week 55 |
| Vital sign, Weight, Height | Day 2 - 21 | Day 14 | Week 2 |
| | Day 22 - 35 | Day 28 | Week 4 |
| | Day 36 - 49 | Day 42 | Week 6 |
| | Day 50 - 80 | Day 56 | Week 8 |
| | Day 81 - 150 | Day 105 | Week 15 |
| | Day 151 – Date of first dose of double-blind IMP (or Date of randomization, if first dose date is missing) if patient is randomized; Day 151 – Day 203 if | Day 196 | Week 28/Beginning of Part II |

| Assessment | Study Day Window | Scheduled day | Scheduled Visit/Week |
|---|---|---|---|
| | patient is not randomized | | |
| | Day after Part II first dose (or Date of randomization, if first dose date is missing) - Week 30 visit date (or Day 217 if subject terminated before Week 30 visit) | Day 210 | Week 30 |
| | Day 218 - Day 231 | Day 224 | Week 32 |
| | Day 232 - 262 | Day 238 | Week 34/Part III |
| | Day 263 - 332 | Day 287 | Week 41 |
| | Day 333 - 382 | Day 378 | Week 54 |
| | ≥Day 383 | Day 385 | Week 55 |
| ECG | Day 2 - 42 | Day 28 | Week 4 |
| | Day 43 - 126 | Day 56 | Week 8 |
| | Day 127 - 287 | Day 196 | Week 28 |
| | ≥ Day 288 | Day 378 | Week 54 |
| Chemistry/ Hematology/ Urinalysis | Day 2 - 126 | Day 56 | Week 8 |
| | Day 127 - 287 | Day 196 | Week 28 |
| | ≥ Day 288 | Day 378 | Week 54 |

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

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

## 6.5. Pooling of Centers

Patients will not be pooled by centers.

# 7. Demographic, Other Baseline Characteristics and Medication

## 7.1. Patient Disposition and Withdrawals

Descriptive statistics of frequency and percentage will be presented overall in one column. The ITT Analysis Set will be used as the denominator for calculating percentages.

The following data will be summarized:

- Total patients enrolled (only frequency);
- Patients enrolled but not treated (and the reason);
- Patients in the ITT and Safety Analysis Sets. Only overall will be presented;
- Patients who withdraw from the study (and reason for withdrawing) before randomization (during Part I);
- Patients randomized in Part II;
- Patients who complete the randomized drug withdrawal period (Part II);
- Patients who withdraw from the study (and reason for withdrawing) during randomized drug withdrawal period (during Part II);
- Patients who complete the study;
- Patients who withdraw from the study (and reason for withdrawing) after randomized drug withdrawal period (during Part III).

In addition, Part II disposition will be summarized. Table will include patients in the RWITT, RWSAF, RWmITT, and RRWmITT populations, separately by treatment. Percentages for RWSAF, RWmITT, and RRWmITT will be computed using the number of subject in the RWITT population as denominator. The following data will be summarized:

- Total patients in the RWITT population (only frequency);
- The RWSAF, RWmITT, and RRWmITT populations by treatment;
- Patients who complete the randomized withdrawal period;
- Patients who withdraw from the study (and reason for withdrawing) during the randomized withdrawal period (Part II).

A listing of study completion will be provided for the ITT Analysis Set. A listing for analysis dataset with reason patient is excluded from the analysis set will also be provided for all patients enrolled.

## 7.2. Demographic and Other Baseline Characteristics

Patient demographics and baseline characteristics will be examined. Summaries for demographics and baseline characteristics will be presented for the ITT and Safety Analysis Sets, and the RWSAF, RWmITT, RRWmITT populations. Unless otherwise specified, for all summaries for ITT and Safety Analysis Sets, 30047 baseline will be used and table will be presented in one overall column, and for all summaries based on the RWSAF, RWmITT, RRWmITT populations, randomized withdrawal baseline will be used and table will be presented by treatment arm.

BMI will be computed as:

BMI ($kg/m^2$) = Weight at baseline (kg) for ITT and Safety Analysis Sets (or randomized withdrawal baseline for RWSAF, RWmITT, and RRWmITT populations) /(Height at baseline for ITT and Safety Analysis Sets [or randomized withdrawal baseline for RWSAF, RWmITT, and RRWmITT populations] $[m]^2$).

In addition, normal age and sex-based z-scores and percentiles for BMI will be determined using the WHO growth charts. Age and sex-based BMI categories includes: Underweight (< 5 percentile), Normal (≥ 5 - < 85 percentile), Overweight (≥ 85 - < 95 percentile), Obese (≥ 95 percentile). Age at baseline for ITT and Safety Analysis Sets (or randomization withdrawal baseline for RWSAF, RWmITT, and RRWmITT populations) will be used.

Variables below will be included in the summary:

- Continuous variables at baseline or randomized withdrawal baseline: patient age, weight, height, body mass index (BMI), BMI World Health Organization (WHO) adjusted z-scores and percentile, time from Tourette syndrome diagnosis to the date of informed consent in current study in years and baseline TTS of YGTSS.
- Categorical variables at baseline or randomized withdrawal baseline: patient sex, race, ethnicity, country, age group (6-11 years; 12 –18 years), weight group (20-<30 kg, 30-<40 kg, or ≥40 kg), sex, race, ethnicity, BMI categories.
- Categorical variables at parent baseline: age group (6-11 years or 12 – 16 years), use of a strong CYP2D6 inhibitor (Yes/No), CYP2D6 genotype (Poor CYP2D6 metabolizer/ Non-poor CYP2D6 metabolizer), and CYP2D6 impairment status (Impaired/Not impaired).

Refer to Section 6.2.1 for the definiations of all baselines.

Continuous variables will be summarized using descriptive statistics. Categorical variables will be summarized using frequency and percentage for each category. Missing categories will be presented if necessary.

## 7.3. Medical History

Medical and psychiatric history, including dates of diagnoses and procedures and whether the condition is ongoing, if applicable, will be collected. Each condition will be recorded as a verbatim term, date of onset, date resolved, and a checkbox that indicates ongoing conditions. For patients from Study TV50717-CNS-30046 and TV50717-CNS-30060, The medical and psychiatric history form from the parent study will be copied over to TV50717-CNS-30047. Adversed events that started in the parent study will also be carried over to TEV50717-CNS-30047 medical history page and summarized as part of medical history. Psychiatric and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.

Medical and surgical history will be summarized for the Safety Analysis Set and the RWSAF population by system organ class (SOC) and MedDRA preferred term (PT). Patient data will be listed.

## 7.4. Prior Medication and Other Therapies

Any prior medications will be entered manually by the sites from IMP administration in the parent study to follow-up. Medications will be coded according to the WHO Drug Version: June 2017. Preferred drug name, Anatomical/ Therapeutic/ Chemical (ATC) class will be reported for inclusion in the database.

Medication summaries based on ATC level 3 and the preferred drug names will be produced for the Safety Analysis Set. The summaries will present the frequency and percentage of patients who used any medication in an ATC class, or any medication based on a single preferred drug name. Medication summaries will be sorted by descending total frequency of ATC class and by PT within ATC class. Patients will be counted only once for each medication class and each preferred drug name.

### 7.4.1. Prior Medication

Prior medications and therapies will include all medications stopped before the first day of study drug administration. Medications stopped during Part I will be considered as prior medications for summary of Part II. Prior medication will be summarized by the ATC level 3 and preferred name for the Safety Analysis Set and the RWSAF population. Same summary will be repeated for prior antidepressant and ADHD medication use. These medications are identified by the ATC codes of:

ADHD medications:
N-NERVOUS SYSTEM
N06-PSYCHOANALEPTICS
N06B-PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS
N06BA-Centrally acting sympathomimetics
N06BC-Xanthine derivatives
N06BX-Other psychostimulants and nootropics.

Antidepressant:
N-NERVOUS SYSTEM
N06-PSYCHOANALEPTICS
N06A-ANTIDEPRESSANTS
N06AA-Non-selective monoamine reuptake inhibitors
N06AB-Selective serotonin reuptake inhibitors
N06AF-Monoamine oxidase inhibitors, non-selective
N06AG-Monoamine oxidase A inhibitors
N06AX-Other antidepressants.

### 7.4.2. Other Therapies

Prior non-pharmacological treatment will be collected in the CRF. Type of treatment/procedure and indication will be summarized.

Prior pharmacological treatment given for TS will be summarized. Table will include number of patients with previous treatment given for TS, total duration of treatment, and best response to treatment. For an ongoing treatment, date of informed consent will be used to compute duration.

Prior non-pharmacological treatments will be listed.

# 8. Efficacy

All assessments in the Parts I and III combined are exploratory in nature and no inferential statistics will be applied; however, inferential statistics will be applied to the efficacy endpoint in the Part II. In general, all efficacy endpoints will be included in the efficacy analyses for the Parts I and III combined based on ITT Analysis Set. Summary for the Parts I and III combined will include one column for all patients and will not include the assessments during Part II. Efficacy endpoints that are assessed in both Parts I and III and in Part II will be presented in two sets of the tables: one for Parts I and III combined, and one for Part II.

## 8.1. Efficacy Assessment and Time Points

### 8.1.1. [redacted]

[redacted]

### 8.1.2. [redacted]

[redacted]

### 8.1.3. Tourette Syndrome-Patient Global Impression of Impact (TS-PGII)

The TS-PGIS is administered on baseline (i.e., 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. Input from the caregiver/adult is permitted.

The TS-PGII is a single-item questionnaire that asks the patient to assess the degree of impact due to current tics. The TS-PGII uses a 5-point scale, ranging from not at all (1) to very much (5), to assess overall response to therapy. In general, patient-rated global measures of change have face validity and have been shown to correlate with disability for a number of chronic conditions.

### 8.1.4. [redacted]

[redacted]

The Tic-free Interval is a 3-item, self-report questionnaire assessing the average number of minutes between tics in patients with TS. Patients rate their symptoms on a 1-to-5 scale, ranging from 1 or more days tic-free (1) to less-than-5-minutes tic-free (5), on their best, worst, and typical days.

8.1.5. [redacted]

8.1.6. [redacted]

## 8.2. Efficacy Endpoint and Analysis

The following efficacy endpoint will be assessed in Part II and included as key secondary endpoint:

- The change in the TTS of the YGTSS from randomized withdrawal baseline (Week 28) to week 30, with the primary analyses and sensitivity testing done as described in Section 8.2.1.

The following efficacy endpoint will be assessed in Part II and included as exploratory secondary endpoint:

- [redacted]
- [redacted]

The following exploratory efficacy endpoints will be assessed in Parts I and III at the visits in which the data is collected:

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

### 8.2.1. The change in the TTS of the YGTSS from randomized withdrawal baseline to Week 30

The change will be derived as the assessment value at Week 30 minus the value at the randomized withdrawal baseline (Week 28).

The observed values at the randomized withdrawal baseline (Week 28) and Week 30, and the change in the TTS of the YGTSS from the randomized withdrawal baseline to Week 30 will be summarized by randomized treatment.

An analysis of covariance (ANCOVA) model will be used as the primary analysis model with the change from Week 28 to Week 30 in YGTSS TTS as the dependent variable, treatment group and age group as fixed effect, and the randomized withdrawal baseline as covariate. The primary analysis will be based on the RRWmITT population. SAS PROC MIXED will be used to carry out this analysis. The SAS code for this test is as follows:

```
proc mixed;
  class arm avisitn agegrp;
  model chg=arm base agegrp;
  lsmeans arm / diff cl stderr;
run;
```

The least square (LS) mean and standard error for the treatment groups, and the LS mean difference, 95% confidence interval (CI), and p-value for the comparison (TEV-50717 vs. placebo) will be presented at week 30. The LS mean of the change in TTS from week 28 to week 30 will be compared using a 2-sided test at the alpha=0.05 level of significance.

For sensitivity analysis, the same analysis will be repeated for the RWmITT population and a subpopulation of the RRWmITT who had a ≥35% reduction in the TTS from the parent study baseline to Week 28.

All summary and analyses will be repeated for each of the age group at entry into the parent study: 6- 11 years and 12- 16 years.

#### 8.2.2. The percent change in the TTS of the YGTSS from randomized withdrawal baseline to Week 30

The same analysis as in Section 8.2.1 will be performed with the percent change used as outcome. No formal hypothesis testing will be done. Nominal p-value will be presented for this exploratory purpose.

#### 8.2.3. Increase in TTS of the YGTSS by ≥20% from randomized withdrawal baseline to week 30

Frequency and percentage of patients with increase ≥20% from randomized withdrawal baseline to week 30 will be summarized. The binary outcome will be analyzed using logistic regression. SAS PROC LOGISTIC will be used to carry out this analysis. The SAS code for this test is as follows:

```
proc logistic;
  class arm avisitn agegrp/param=glm;
  model chg=arm base agegrp;
  lsmeans arm / diff cl stderr;
run;
```

#### 8.2.4. The Analysis of the Change Scores in Parts I and III Combined

These change scores are included as the exploratory endpoints for Parts I and III combined: the change in the TS-CGI score, the TS-PGII score, the C&A-GTS QOL ADL subscale score, the TTS of the YGTSS, the TS-PGIS score, the YGTSS impairment score, the MTSS of the YGTSS, the VTSS of the YGTSS, the GSS of the YGTSS, VAS in the C&A-GTS QOL score, CY-BOCS scores, and the C&A-GTS QOL total

and subscale score, tic-free score, the percent change in the TTS of the YGTSS from baseline to each visit.

These changes will be derived as the assessment value minus baseline. The observed values and the changes from baseline will be summarized at each visit in which the scale is administered, including Week 28, but not Week 30 visit if assessed. The summary will be based on the ITT Analysis Set.

#### 8.2.5. Proportion of Patients with Improvement on the TTS of the YGTSS and TS-CGI for Parts I and III Combined

Proportion of patients who have ≥25% reduction, ≥35% reduction from baseline on the TTS of the YGTSS to each visit, ≥25% reduction from baseline of the parent study to each visit, a reduction of ≥1 point in the TS-CGI score from baseline to each visit will be analyzed. Frequency, and proportion will be presented at each visit for the ITT Analysis Set in the Parts I and III combined. Summary tables will include one column for all patients. All visits, including Week 28, will be included, but not Week 30.

# 9. Safety

For by-visit safety endpoints, e.g. vital sign, CDI-2, summaries will be presented for:

- The observed values and the change from baseline. The change will be derived as the observed value at the specific visit minus the baseline. Week 30 assessments will not be included. Analyses will be based on the Safety Analysis Set with an overall column.
- The observed values and the change from Week 28 to Week 30. The change will be derived as the observed value at Week 30 minus the randomized withdrawal baseline. Tables will be based on the RWSAF population and presented by actual treatment received during randomized drug withdrawal period and overall. This will only be included if assessment is performed at Week 30 visit.

For safety endpoints of adverse event and exposure, summary will be presented for:

- Parts I and III combined;
- Part II;
- Parts I, II, and III combined and for each Parts;
- Periods.

The following safety endpoints will be assessed in Parts I and III combined:

- The incidence of adverse events
- The observed values and changes from baseline in vital signs
- The observed values and changes from baseline in the CDI-2
- The observed values in the C-SSRS
- The observed values in ECG parameters and shifts from parent study baseline for clinically significant abnormal findings
- The observed values and changes from baseline in clinical laboratory parameters (hematology, serum chemistry, and urinalysis)

The following safety endpoint will be assessed in Part II:

- The incidence of adverse events;
- The observed values and changes from randomized withdrawal baseline (Week 28) in vital signs;
- The observed values and changes from randomized withdrawal baseline (Week 28) in the CDI-2;
- The observed values in the C-SSRS.

## 9.1. Extent of Exposure

Descriptive statistics will be presented for:

- Duration of exposure to study medication in Parts I, II and III combined, based on Safety Analysis Set and Weeks on treatment using the categories ≤28 weeks, >28 to ≤54 weeks, >54 weeks;
- Duration of exposure to study medication in each Part;
- Duration of exposure to study medication in Parts I and III combined, based on Safety Analysis Set and Weeks on treatment using the categories ≤28 weeks, >28 to ≤52 weeks, >52 weeks;
- Duration of exposure in Part II based on the RWSAF Population.

## 9.2. Treatment Compliance

Study drug administration and accountability during open-label portion collect information of the assigned total daily dose in mg, date time of the first and the last dose, and the number of pills taken per dose strength (6, 9, and 12 mg). Study drug administration and accountability during blinded portion collect information of study week, date time of the first and the last dose, number of pills taken per bottle. The compliance is computed in sequence below:

The total number of pills taken=sum (the number of pills taken from all bottles dispensed, identified by med ID);
The number of pills expected = sum (the number of pills should be taken per schedule for all bottles dispensed (Table 4 and Table 5), identified by med id or bottle dose strength) ;
Treatment compliance (%) = 100*(total number of doses taken / number of doses expected to be used).

**Table 4: Part I Titration, Maintenance Phases and Part III Maintenance Administration Instructions**

| Daily Dose | First Kit Type Needed | | Second Kit Type Needed | | Administration Instructions |
|---|---|---|---|---|---|
| | # Tablets Per Day | Tablet Strength | # Tablets Per Day | Tablet Strength | |
| 6 mg | 1 | 6 mg | n/a | n/a | Enrollment Day 1 In Clinic:<br>Day 1: 6 mg: Take 0 tablets AM and 1 tablet PM<br>Day 2–7: 6 mg: Take 1 tablet AM and 0 tablets PM<br>All Other Visits: 6 mg: Take 1 tablet AM and 0 tablets PM |
| 6 /12 mg | 1 | 6 mg | n/a | n/a | Day 1: 6 mg: Take 0 tablets AM and 1 tablet PM<br>Day 2: 6 mg: Take 1 tablet AM and 0 tablets PM<br>Days 3–7: 6 mg: Take 1 tablet AM and 1 tablet PM |
| 12 mg | 2 | 6 mg | n/a | n/a | 6 mg: Take 1 tablet AM and 1 tablet PM |
| 18 mg | 2 | 9 mg | n/a | n/a | 9 mg: Take 1 tablet AM and 1 tablet PM |
| 24 mg | 2 | 12 mg | n/a | n/a | 12 mg: Take 1 tablet AM and 1 tablet PM |
| 30 mg | 2 | 6 mg | 2 | 9 mg | 6 mg: Take 1 tablet AM and 1 tablet PM<br>9 mg: Take 1 tablet AM and 1 tablet PM |
| 36 mg | 4 | 9 mg | n/a | n/a | 9 mg: Take 2 tablets AM and 2 tablets PM |
| 42 mg | 2 | 9 mg | 2 | 12 mg | 9 mg: Take 1 tablet AM and 1 tablet PM<br>12 mg: Take 1 tablet AM and 1 tablet PM |
| 48 mg | 4 | 12 mg | n/a | n/a | 12 mg: Take 2 tablets AM and 2 tablets PM |

**Table 5: Part II and Part III Re-Titration or Blinded Maintenance Period Administration Instructions**

| Last Dose Dispensed in Part A Maintenance | Bottle A Dispensed | Bottle B Dispensed | Dispensation Instructions |
|---|---|---|---|
| 6 mg | Yes | n/a | Bottle A: Take 1 tablet AM and 0 tablet PM |
| 12 mg | Yes | n/a | Bottle A: Take 1 tablet AM and 1 tablet PM |
| 18 mg | Yes | n/a | Bottle A: Take 1 tablet AM and 1 tablet PM |
| 24 mg | Yes | n/a | Bottle A: Take 1 tablet AM and 1 tablet PM |
| 30 mg | Yes | n/a | Bottle A: Take 1 tablet AM and 1 tablet PM |
| 36 mg | Yes | n/a | Bottle A: Take 1 tablet AM and 1 tablet PM |
| 42 mg | Yes | Yes | Bottle A: Take 1 tablet AM and 1 tablet PM<br>Bottle B: Take 1 tablet AM and 1 tablet PM |
| 48 mg | Yes | Yes | Bottle A: Take 1 tablet AM and 1 tablet PM<br>Bottle B: Take 1 tablet AM and 1 tablet PM |

If a patient does not return a pill bottle, it will be assumed that the patient took no study drug from that bottle for the purposes of calculating compliance. If the first or last dose date is missing, the date of the previous visit and the day before current visit will be used as the first and last dose. The total assigned daily dose is not collected for the blinded period and the last assigned dose before Week 28 will be used. Compliance will also be summarized by categories <80%, 80% - < 105%, and >105%. Compliance will be summarized for Parts I and III combined based the Safety Analysis Set, Part II, based on the RWSAF Population.

### 9.3. Concomitant Medication

A concomitant medication is any medication that starts prior to first day of study drug administration and continues into treatment period, or started after the first dose of IMP. In the case of completely missing stop date and medication is not ongoing, medication will be assumed to be concomitant.

Concomitant medication summaries based on ATC level 3 and the preferred drug names will be produced for the Safety Analysis Set. The summaries will present, the frequency and percentage of patients who used any medication in an ATC class, or any medication based on a single preferred drug name. Medication summaries will be sorted by descending total frequency of ATC class and by PT within ATC class. Patients will be counted only once for each medication class and each preferred drug name. Concomitant medication will be summarized for entire treatment period in one overall column. No by age group summary will be included.

In addition, ADHD and antidepressant medication(see Section 7.4.1 for ATC code list) change will be summarized for:

- Proportion of patients with requiring increased medication;
- Proportion of patients requiring decreased/stopped medication;

Proportion of patients with medication switch.The proportion of patients who alter their medication. A separate listings will be provided for these patients with all ADHD and antidepressant medications.

All summary tables will be presented for Parts I and III combined, and Part II.

## 9.4. Adverse Events

Adverse events will be collected and recorded from the time a patient signs the TV50717-CNS-30047 informed consent to the end of follow-up period.

For all AEs, preferred AE terms and system organ class (SOC) will be coded using terminology from the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1.

A treatment emergent adverse event (TEAE) is defined as an AE that begins after the first administration of study medication or existing AEs that worsen after the first dose of study medication. All reported AEs will be listed, but only TEAEs will be summarized in tables.

Drug related AEs will be considered those to be reasonable possibility based on the investigators assessment. Missing relationship will considered as “Related”.

Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs and PTs within SOCs presented in descending order of patient incidence.

AE summary tables are listed below:

- An overall summary of the number and percentage of patients reporting any TEAEs, serious TEAEs, treatment-related TEAEs, serious treatment-related TEAE, any TEAEs leading to study drug discontinuation, any TEAEs leading to patient dose interruption, any TEAEs leading to patient dose reduction, and TEAEs leading to death. Same summaries will also be presented by each of the age group at entry into the parent study: 6- 11 years and 12- 16 years and parent study baseline CYP2D6 impairment status (Impaired/Not impaired).
- TEAEs overall and by SOC and PT;
- TEAEs by severity, overall and by SOC and PT. Missing severity, if any, will be assumed as “severe”;
- Serious TEAEs, overall and by SOC and PT;
- Serious and related TEAEs, overall and by SOC and PT;
- TEAEs by relationship to study treatment, overall and by SOC and PT
- TEAEs leading to study drug discontinuation, overall and by SOC and PT;
- TEAEs leading to dose interruption, overall and by SOC and PT;
- TEAEs leading to dose reduction, overall and by SOC and PT;
- Most common TEAEs, overall and by PT. Most common TEAEs are defined as TEAEs that occur in > 4% of the patients;
- SMQs for suicide/self-injury and depression (exclude suicide and self-injury) and Parkinson-like events.

All AEs will be allocated to Parts (Section 6.2.6) or Periods (Section 6.2.7), depending on in which Part or Period the TEAEs occurs. Tables will be presented by Parts or Periods as below:

- Parts I and III combined, based on the Safety Analysis Set. The events that occurred in Part II will not be included. Table will contain one overall column. All tables will include number, frequency of patients with the event, and EAIR. All AE tables will be prepared for Part I and III combined.

- Part II is based on the RWSAF population and presented by the actual treatment received during the randomized withdrawal period. Table will include number and frequency of patients with the event. All AE tables will be preared for Part II.
- Parts I, II, and III combined, based on the Safety Analysis Set. Table will contain one overall column. The Parts I, II, and III combined tables will be presented for entire study and by each Part. All tables will include number, frequency, and the EAIR. The overview of AEs, AEs by SOC and preferred terms, and the SMQ summaries will be presented for Parts I, II, and III combined.
- Periods, based on the Safety Analysis Set. Table will contain one overall column. All tables will include number, frequency, and the EAIR. The overview of AEs and AEs by SOC and preferred terms will be presented by periods.

For summary of patient, the following rules will apply:,

1. Patients having more than 1 event with the same PT will be counted once for that term.
2. Patients having more than 1 event with the same SOC will be counted once for each event and once for that SOC.
3. For tabulations by severity, only a patient's most severe event within the category (e.g. overall, SOC, PT) will be counted; similarly, for tabulations by relationship, only a patient's most related event within a category will be counted. The denominator for percentages will be the number of patients in Safety Analysis Set for the given treatment group or overall (i.e., the N's for the columns).

For the summary of incidence rate, all events will be included.

Listings will be provided for all AEs and the following subsets:

- All TEAEs
- Serious TEAEs
- TEAEs leading to study drug discontinuation
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- TEAEs leading to death.

### 9.5. Laboratory Evaluations

Laboratory tests will include chemistry panel, hematology panel, and urinalysis testing. Laboratory tests will be performed per Table 3. A list of laboratory tests is included in Table 6.

The observed values (in SI units) and the change from the Part I baseline to all post–baseline visits will be summarized. For hematology and chemistry panel, result will also be categorized as "Normal", "Low", or "High" based on their normal ranges. For urinalysis results, tests will be classified as "Normal" or "Abnormal". Shift tables comparing laboratory test results from baseline to each post-baseline visits will be presented.

All laboratory data will be listed. For hematology, chemistry, columns will be included for normal ranges and individual abnormal laboratory values will be flagged. Listing for urinalysis will include the microscopic examination provided for patients who have a positive result from the urinalysis dipstick evaluation.

**Table 6: List of Laboratory Tests**

| Serum Chemistry | Hematology | Urinalysis |
|---|---|---|
| calcium<br>phosphate<br>sodium<br>potassium<br>chloride<br>creatinine<br>glucose<br>magnesium<br>blood urea nitrogen (BUN)<br>total cholesterol<br>uric acid<br>alanine aminotransferase (ALT)<br>aspartate aminotransferase (AST)<br>lactate dehydrogenase (LDH)<br>alkaline phosphatase (ALP)<br>bicarbonate or carbon dioxide<br>total protein<br>albumin<br>total bilirubin<br>direct bilirubin | hemoglobin<br>hematocrit<br>red blood cell (RBC) count<br>mean cell volume<br>platelet count<br>white blood cell (WBC) count, and differential count<br>– absolute neutrophil count (ANC)<br>– polymorphonuclear leukocytes (neutrophils)<br>– lymphocytes<br>– eosinophils<br>– monocytes<br>– basophils | protein<br>glucose<br>ketones<br>blood (hemoglobin)<br>pH<br>specific gravity<br>microscopic<br>– bacteria<br>– RBCs<br>– WBCs<br>– casts<br>– crystals |

### 9.6. Pregnancy

Human chorionic gonadotropin tests in urine or serum will be performed for all females who are postmenarchal or ≥12 years of age as detailed in Table 3 and if clinically indicated. The pregnancy data will be presented in a data listing.

### 9.7. Vital Signs

Vital signs will be measured at time points per Table 3. Measurements of vital signs will include measurement of pulse, blood pressure (BP), weight, body temperature, and respiratory rate. Pulse and BP in supine or semi-erect/seated position will be measured in each scheduled or unscheduled visits. In addition, standing BP and pulse will be taken at selected visits per Table 3. BMI will be computed similarly as in Section 7.2 at weeks that both weight and height are measured (see Table 3). Normal age and sex-based z-scores, percentiles for BMI, and BMI categories will also be determined using the WHO growth charts similarly as in Section 7.2. Age at the specific visit will be used.

Orthostatic systolic and diastolic BP and pulse will be calculated as supine or semi-erect/seated measurement – standing measurement. Orthostatic hypotension (determined by blood pressure measurements only) is defined as having either a ≥ 20 mmHg reduction from supine to standing position in systolic blood pressure (SBP) or ≥ 10 mmHg reduction from supine to standing position in diastolic blood pressure (DBP) or both. Orthostatic tachycardia is defined as pulse increase ≥ 20 bpm from supine to standing position.

Observed values, change from baseline, for each vital sign parameter and position will be summarized at each visit.

In addition, orthostatic hypotension or orthostatic tachycardia occurrences, and the markedly abnormal post-baseline vital signs results will also be summarized for patients with at least one markedly abnormal value during the Parts I and III combined according to criteria specified in Table 7. A listing will be provided for all markedly abnormal vital signs. A shift table for BMI age and set adjusted categories will be presented comparing shifts from the baseline visit to end of treatment. Percentages will be based on the number of patients with a non-missing value for both the baseline and post-baseline visit for the given vital sign.

**Table 7: Criteria for Markedly Abnormal Vital Sign Parameters by Age**

| Parameter (unit) | Age (years old) | Markedly Low | Markedly High |
|---|---|---|---|
| SBP (supine, standing) (mmHg) | 6-12 | Value ≤ 70 and≥ 20 decrease from baseline | Value ≥ 120 and ≥ 20 increase from baseline |
| | 13-18 | Value ≤ 90 and ≥ 20 decrease from baseline | Value ≥ 135 and ≥ 20 increase from baseline |
| DBP (supine, standing) (mmHg) | 6-12 | Value ≤ 40 and ≥ 15 decrease from baseline | Value ≥ 80 and ≥ 15 increase from baseline |
| | 13-18 | Value ≤ 50 and ≥ 15 decrease from baseline | Value ≥ 90 and ≥ 15 increase from baseline |
| Pulse rate (supine, standing) (bpm) | 6-10 | Value ≤ 60 and ≥ 15 decrease from baseline | Value ≥ 135 and ≥ 15 increase from baseline |
| | 11-18 | Value ≤ 50 and ≥ 15 decrease from baseline | Value ≥ 120 and ≥ 15 increase from baseline |
| SBP orthostatic criteria (mmHg) | ~ | ≥ 20 decrease from supine to standing position | NA |
| DBP orthostatic criteria (mmHg) | ~ | ≥ 10 decrease from supine to standing position | NA |
| Pulse rate orthostatic criteria (bpm) | ~ | NA | ≥ 20 increase from supine to standing position |
| Temperature (˚C) | ~ | NA | Value ≥ 38.3°C and ≥0.8°C increase from baseline |

Note: ~ means that the abnormal range is applicable for all patients within age group: 6 to 17 years old.

Vital signs data will be provided in a data listing.

## 9.8. ECG

Assessment of Standard 12-lead ECG are obtained at visits per Table 3. A central ECG Standard 12-lead ECG will record heart rate (HR), PR interval, RR interval, QT interval, Fridericia's corrected QT interval (QTcF), and QRS duration. The overall ECG assessment will be centrally reported as "Normal" or "Abnormal". If a post-baseline QTcF value >500 msec or change from baseline >60 msec is found, the investigator should repeat the ECG assessment twice. In this case, the confirmed QTcF, defined as the average of all 3 ECG values at the visit, will be used for summary.

Baseline for ECG assessment is the parent study baseline.

Observed results of each ECG parameter and change from baseline will be summarized by visit using descriptive statistics.

In addition, for QTcF, average baseline confirmed QTcF (the average of the parent study screening and baseline QTcF), and the change from average baseline will be summarized visit using descriptive statistics.

QTcF values will be classified as having QTc prolongation according to the following conditions.

| QTc Prolongation |
|---|
| Confirmed QTcF >450 msec |
| Confirmed QTcF>480 msec |
| Confirmed QTcF>500 msec |
| Increase from baseline QTcF ≥ 60 msec |
| Increase from average baseline confirmed QTcF ≥ 60 msec |
| Increase from baseline QTcF ≥ 30 msec |
| Increase from average baseline confirmed QTcF ≥ 30 msec |

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

A shift table comparing the overall ECG assessment from baseline to each visit will be presented.

In addition, the markedly abnormal post-baseline ECG results will also be summarized for patients with at least one markedly abnormal value during the treatment period. The summary will be completed by the age groups (6 - < 8 years, 8 - < 12 years, and 12 - < 16 years) at the time of the individual assessment.

Criteria for markedly abnormal values used in the study are presented in Table 8.

**Table 8: Criteria for Abnormal ECG Parameters by Age**

| ECG parameter (unit) | Age (years old) | Abnormally Low | Abnormally High |
|---|---|---|---|
| HR (bpm) | 6 to <8 | < 65 | > 115 |
| | 8 to <12 | < 55 | > 110 |
| | 12 to <16 | < 50 | > 105 |
| | ≥16 | < 50 | > 100 |
| PR interval (msec) | 6 to <8 | -- | > 160 |
| | 8 to <12 | -- | > 175 |
| | 12 to <16 | -- | > 180 |
| | ≥16 | -- | > 200 |
| QRS interval (msec) | 6 to <8 | -- | > 100 |
| | 8 to <12 | -- | > 105 |
| | 12 to <16 | -- | > 110 |
| | ≥16 | -- | > 120 |

## 9.9. Physical Examination

Physical examinations are performed at visits per Table 3. Physical examinations will be listed.

## 9.10. Neurological Examinations

Neurological examinations will be performed at visits per Table 3. Neurological examinations will be listed.

## 9.11. Children's Depression Inventory, Second Edition (CDI-2)

The CDI-2 (parent and self-report versions) is administered per Table 3. 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 CDI-2 Self-report version contains 6 subscales (emotional problem, negative mood/physical symptoms, negative self-esteem, functional problems, ineffectiveness, and interpersonal problems). The raw score is the sum

of all subscales scores, ranging from 0 to 56, with higher score indicating more severe depressive symptoms. The raw score is normalized to T-score (range: 40-90) based on patient's age and gender.

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 CDI-2 parent version contains 2 subscales (emotional problems and functional problem). The raw score is the sum of the 2 subscales, ranging from 0 to 51, with higher score indicating more depression-related behaviors observed in their children. The raw score is normalized to T-score (range: 40-90) based on patient's age and gender.

The CDI-2 parent version and self-report versions subscale scores, raw scores, and self-report version T scores will be summarized at each visit.

## 9.12. ADHD Symptoms

Based on input from the TEV-50717 Tourettes Syndrome Scientific Advisory Board (SAB), which contains experts in the area of child psychiatric and in the attempt to identify possible symptoms consistent with ADHD symptomatology, the items below from C&A-GTS-QOL were chosen:

Item 11 – Difficulty concentrating;

Item 12 – Had problems with your memory;

Item 13 – Lost or misplaced important things;

Item 14 – Had difficulty finishing your tasks once you started them;

Item 20 – Felt fidgety ((Version: Age 6-12 Years) or Felt restless or fidgety (Version: Age 13-18 Years).

The item below from CDI-2 self version was chosen:

Item 22 – Schoolwork.

Summary statistics will be provided to the observed values and change from baseline for Parts I and III combined based safety analysis set. This analyses are only exploratory and for signal detection purpose.

## 9.13. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS children's since last visit (SLV) scale is administered per Table 3. Patients will be placed into categories for suicidal ideation and for suicidal behavior based on their responses to various questions.

The suicidal ideation categories will be determined as follows by examining the response to the 5 questions under Suicidal Ideation.

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

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

| Type | Section |
|---|---|
| Suicidal behavior | (6) Preparatory Acts or Behavior – if response to Preparatory Acts and Behavior is Yes and responses to Actual Attempt, Interrupted Attempt, Aborted Attempt, and Completed Suicide are No<br><br>(7) Aborted Attempt – if response to Aborted Attempt is Yes and responses to Actual Attempt, Aborted Attempt, and Completed Suicide are No.<br><br>(8) Interrupted Attempt – if response to Interrupted Attempt is Yes and response to Aborted Attempt, and Completed Suicide are No.<br><br>(9) Actual Attempt – if response to Actual Attempt is Yes and Completed Suicide is No.<br><br>(10) Completed Suicide - if response to Completed Suicide is Yes<br><br>(0) None – if responses to all the above 4 questions are No. |

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

The frequency and percentage of suicidal ideation, suicidal behavior, suicidal ideation or behavior, and self-injurious behavior without suicidal intent from SLV version will be summarized by visit. Separate summaries will be prepared for the Parts I and III combined for all patients based on the Safety Analysis Set, and Part II by treatment group for the RWSAF Population.

Frequency and severity of suicidal ideation or behavior will also be summarized, using a shift table to examine changes in above C-SSRS scores from baseline compared to the worst (highest) category in the Parts I and III combined and Week 28 to Week 30 visit for Part II.

# 10. Interim Analyses

One interim analysis for Part I data is planned after 100 patients completed Part I. No blinded data from Part II will be included in the interim analysis, and hence, no alpha adjustment is needed for the analysis of the key efficacy endpoint in Part II.

## 10.1. Endpoints

The endpoints that will be included in the interim analysis include:

Safety Endpoints:

The following safety endpoints will be assessed in Part I (up to and including Week 28 visit):

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

Exploratory Efficacy Endpoints:

The following exploratory endpoints will be assessed in Part I at the visits in which the data is collected (up to and including Week 28 visit):

[redacted]

### 10.2. Demographic, Other Baseline Characteristics and Prior Medication

Demographic, other baseline characteristics and medication included with interim will include:

- Disposition for Part I as described in Section 7.1. Only Part I will be included;
- Demographics and other baseline characteristics for the ITT and Safety Analysis Set (Section 7.2);
- Medical History for the Safety Analysis Set (Section 7.3);
- Prior Medication for Safety Analysis Set (Section 7.4).

### 10.3. Safety

All safety endpoints will be presented similarly to Section 9. TEAE occurred in Part I and resolved in Part II or Part III will be included and will be considered as ongoing.

### 10.4. Efficacy

All efficacy endpoint will be presented similarly to Section 8.2.4 and Section 8.2.5.

All efficacy endpoints are exploratory. Only assessments until Week 28 will be included.

## 11. Changes from Analysis Planned in Protocol

Summary based on the ITT Analysis Set will include one column for all patients. In protocol, analyses based on the ITT Analysis Set are by randomized treatment and “Not Randomized” for patients not entered Part II (Protocol Section 9.2.1).

Prior ADHD and antidepressant medications, change in ADHD medications and symptoms are added.

Two efficacy exploratory endpoints are added to Part II:

[redacted]

Additional exploratory endpoints are added to Parts I and III combined:

[redacted]

# 12. Reference List

# 13. Programming Considerations

## 13.1. General Considerations

- One SAS program can create several outputs.
- One output file can contain several outputs.
- Output files will be delivered in Rich Text Format (RTF) format.
- Numbering of TFLs will follow ICH E3 guidance

## 13.2. Table, Listing, and Figure Format

### 13.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

### 13.2.2. Headers

- All output should have the following header at the top left of each page:

  Nuvelution TS Pharma, Inc

  Protocol TV50717-CNS-30047
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

### 13.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C “Table of Contents for Tables Listings and Figures in Statistical Analysis Plan”). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

### 13.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

### 13.2.5. Body of the Data Display

#### 13.2.5.1. *General Conventions*

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

13.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

| Severity Rating | N |
|---|---|
| severe | 0 |
| moderate | 8 |
| mild | 3 |

- Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.
- For continuous variables, if n<5 then only the min, max and median will be presented and mean, SD and SE will not be presented.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

| | |
|---|---|
| n | XX |
| Mean | XXX.X |
| SD | XX.XX |
| SE | XX.XX |
| Median | XXX.X |
| Minimum, Maximum | XXX, X, XXX.X |

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999.

- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Display values that round down to 0.0 as '<0.1%'. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.
- Missing descriptive statistics or p-values which cannot be estimated should be reported as “NE”.
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Details will be described in table footnotes.
- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, whether the patient should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria will be described in footnote.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont.)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

#### 13.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.
- Missing data should be represented on patient listings as either a hyphen (“-”) with a corresponding footnote (“- = unknown or not evaluated”), or as “N/A”, with the footnote “N/A = not applicable”, whichever is appropriate.
- Dates should be printed in ISO format (“YYYY-MM-DD”: 2000-07-01). Missing portions of dates should be represented on patient listings as dashes (2000-07- - -). Dates that are missing because they are not applicable for the patient are output as “N/A”, unless otherwise specified.

- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

13.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.5.5. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Patient specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Source: Listing 16.x.y.z’)..

# 14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output."