Statistical Analysis Plan

A Well-Controlled, Fixed-Dose Study of TEV 50717 (Deutetrabenazine) for the Treatment of Tics Associated with Tourette Syndrome

Study Number TV50717-CNS-30060

NCT03571256

SAP Approval Date: 14 January 2020

Statistical Analysis Plan for Interventional Studies

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

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0.2	14-Jun-2019	[redacted]	Update per sponsor comments
1.0	28-Jun-2019	[redacted]	Update per sponsor comments
1.1	10-Jan-2020	[redacted]	• Update prior medication definition to include only medication stopped before first dose of IMP in Section 7.4.1; • Prior non-pharmacological treatment will only be listed in Section 7,4,2; • Correct SAS code for primary analysis of primary endpoint in Section 8.2.1. Maximum likelihood method will only be used when REML did not converge. • Adding that concomitant medications will be summarized separately for medication started prior to or after the first dose of IMP in Section 9.3; • Adding SMQ of Parkinson-like events to Section 9.4; • SAS code for imputations in Appendix 19.1 – 19.3 are updated to include situation when all patients completed Week 2 assessment and region is added to the imputation models as covariates and add Region1 to proc MI; • Index of tables, listings, figures are corrected. • Add CDI-2 self version item 22 to section 9.12.
2.0	14-Jan-202	[redacted]	• To add Section 3.1 and 3.2 of primary and secondary estimand, and justification of the primary estimand in Section 8.2.2.

Approvals

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

Approvals

Syneos Health Approval

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1. Glossary of Abbreviations

Abbreviation	Description
ADHD	Attention Deficit Hyperactivity Disorder
ADL	Activities of daily living
AE	Adverse Event
α-HTBZ	alpha-dihydrotetrabenazine
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
β-HTBZ	beta-dihydrotetrabenazine
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
[redacted]	[redacted]
CYP	Cytochrome P450
CYP2D6	Cytochrome P450 2D6
ECG	Electrocardiogram
FCS	Fully Conditional Specification
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPSP	Global Subject Safety and Pharmacovigilance
GSS	Global Severity Score

Abbreviation	Description
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
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
PP	Per Protocol
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
QC	Quality Control
QTc	Corrected QT Interval
QTcF	Fridericia's corrected QT interval
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Description
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-Subject Global Impression of Impact
[redacted]	[redacted]
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 and Teva will perform review of all tables, figures and listings before the finalization.

2.2. Timings of Analyses

The primary analysis of safety and efficacy is planned after all patients complete the week 9 follow-up visit and enter the open-label safety extension study TV50717-CNS-30047, or complete week 10 follow-up visit, or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

An independent Data Monitoring Committee (IDMC) will review descriptive summaries of accumulating safety and subject 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

The purpose of the study is to determine whether TEV-50717 is effective in the treatment of tics associated with TS in male and female patients between 6 and 16 years of age.

3.1. Primary Estimand

The primary estimand is the difference in means between TEV-50717 high dose and placebo for the change in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) from baseline to week 8, in the target patient population of children and adolescents with TS who receive at least 1 dose of IMP and have both a baseline and at least 1 post-baseline YGTSS assessment, regardless of whether or not dose reduction, suspension, or treatment discontinuation occurred, and regardless of treatment-related adverse events. For the intercurrent event of study discontinuation, all data collected until time of study discontinuation will be included and a missing at random (MAR) assumption will be hypothesized.

The primary estimand assesses the effectiveness in the reduction of motor and phonic tics associated with TS, focusing on the causal effects attributable to the investigational medicinal product (IMP).

3.2. Secondary Estimands

The secondary estimands are:
(1) the difference in means between TEV-50717 high dose and placebo for the change in the Tourette Syndrome - Clinical Global Impression (TS-CGI) score from baseline to week 8;
(2) the difference in means between TEV-50717 low dose and placebo for the change in the TTS of the YGTSS from baseline to week 8;
(3) the difference in means between TEV-50717 low dose and placebo for the change in the TS-GCI score from baseline to week 8;
(4) the difference in means between TEV-50717 high dose and placebo for the change in the Tourette Syndrome - Patient Global Impression of Impact (TS-PGII) score from baseline to week 8;
(5) the difference in means between TEV-50717 low dose and placebo for the change in the TS-PGII score from baseline to week 8;
(6) the difference in means between TEV-50717 high dose and placebo for the change in the Child and Adolescent Gilles de la Tourette Syndrome - Quality of Life (C&A-GTS-QOL) activities of daily living (ADL) subscale score from baseline to week 8;
(7) the difference in means between TEV-50717 low dose and placebo for the change in the C&A-GTS-QOL ADL subscale score from baseline to week 8,
in the target patient population of children and adolescents with TS who receive at least 1 dose of IMP and have both a baseline and at least 1 post-baseline YGTSS assessment, regardless of whether or not dose reduction, suspension, or treatment discontinuation occurred, and regardless of treatment-related adverse events. For the intercurrent event of study discontinuation, all data collected until time of study discontinuation will be included and a missing at random (MAR) assumption will be hypothesized.

The secondary estimands assess the effectiveness of TEV-50717 high dose and TEV-50717 low dose in the reduction of motor and phonic tics associated with TS and the impact of the reduction in tics on the patients' quality of life as assessed by the clinicians and the patients, focusing on the causal effects attributable to the investigational medicinal product (IMP).

3.3. Primary and Secondary Objectives

3.3.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of fixed doses of TEV-50717 to reduce motor and phonic tics associated with Tourette syndrome (TS).

3.3.2. Secondary Objective(s)

The secondary objective of the study is to evaluate the safety and tolerability of TEV-50717.

3.4. Brief Description

This is a Phase 3, randomized, double-blind, placebo-controlled, 8-week treatment study in which patients with tics associated with TS will be invited to participate. Patients will be randomized to low-dose TEV-50717, high-dose TEV-50717, or placebo (1:1:1). The target dose for each patient receiving TEV-50717 will be based on body weight and cytochrome P450 2D6 (CYP2D6) impairment status at baseline. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer based on blinded assessment of CYP2D6 genotype at baseline. CYP2D6 status will be used by Interactive Response Technology (IRT) for randomization into the study. The overall treatment period will be 8 weeks in duration, including an escalation period of 4 weeks, a maintenance period of 4 weeks, followed by a washout period of 1 week.

Patients who complete the study may be eligible to begin participation in an open-label safety extension study of TEV-50717 (Study TV50717-CNS-30047). For this study, the follow-up period is defined as 1 week of washout for patients who will participate in the open-label safety extension study TV50717-CNS-30047 and 2 weeks after the last dose of Investigational Medicinal Product (IMP) (1 week after the end of the washout period) for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047. Patients not participating in the open-label safety extension study for TEV-50717 will have a follow-up telephone contact for safety evaluation 1 week after the end of the treatment period (2 weeks after their last dose of IMP).

3.5. Patient Selection

3.5.1. Inclusion Criteria

Refer to Protocol Section 4.1 for inclusion criteria.

3.5.2. Exclusion Criteria

Refer to Protocol Section 4.2 for exclusion criteria.

3.6. Determination of Sample Size

It is estimated that approximately 50 patients per arm will enable a power of at least 90% to detect a beneficial effect of 6.5 points or more in the change from baseline to week 8 in TTS when the high-dose TEV-50717 arm is compared to placebo, assuming a standard deviation of 9.5 and a 2-sided type I error rate of 5% after accounting for dropouts.

3.7. Treatment Assignment & Blinding

This is a Phase 3, randomized, double-blind, placebo-controlled, 8-week-treatment study in which patients with tics associated with TS will be invited to participate. Patients will be randomized to either

TEV-50717 (low-dose, high-dose) or matching placebo in a 1:1:1 ratio using an Interactive Response Technology (IRT) based on their baseline weight and CYP impairment status. The patients will be stratified into 2 age groups (6- to 11-years and 12- to 16-years). Patients and investigators will remain blinded to treatment assignment during the study.

3.7.1. Treatment Assignment

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

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

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

3.7.2. Blinding

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

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

Pharmacokinetic data may be assessed during the study. Personnel responsible for bioanalysis will be provided with the randomization code in order to facilitate the analysis. However, the personnel responsible for bioanalysis and pharmacokinetic data analysis will not have access to clinical safety and efficacy data, will not have any interaction with study personnel, and will provide concentration data to other personnel in a manner that will not identify individual patients (i.e., a dummy patient identifier will be linked to an individual patient's concentration data).

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 blinded studies, for adverse events that are defined as: suspected unexpected serious adverse reactions (SUSARs), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the treatment code be revealed (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct, analysis, and reporting of the data.

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. All relevant personnel to receive unblinded data will be identified and their responsibilities documented on the unblinded personnel form. 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.

3.8. Administration of Study Medication

Investigational medicinal product will be administered as follows:

- IMP should be swallowed whole and taken with food (e.g., a snack) and should not be taken on an empty stomach.
- Dosing will be based on body weight and CYP2D6 impairment status at the baseline visit, as shown in Table 1.
- To preserve blinding, 2 tablets will be taken twice daily starting at day 1 per Table 1. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day. Depending on the dose and arm assigned, TEV-50717 tablets and/or placebo tablets will be taken to maintain the blind. A minimum of 6 hours should elapse between doses. If a patient misses a dose and it is within 6 hours of their next dose, the missed dose should be skipped.
- After week 1, dose increases may not occur more frequently than every 5 days.
- The dose of IMP will be escalated weekly during the escalation period, according to Table 1.
- Dose reductions, if required, should be in increments of 6 mg. If more than 1 dose reduction is required for an adverse event, the medical monitor must be notified.
- During the escalation period, the dose of the IMP will be adjusted weekly according to Table 1 to identify a dose level that optimally *reduce*s tics and is well tolerated. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers prespecified by the IRT.

Table 1: Daily Dose of IMP by Baseline body Weight Category, CYP2D6 Impairment, and Study Week

Dose group Baseline weight (kg)	Daily dose (mg) at the start of visit/week			
	Week 1 (Days 1-7)	Week 2 (Days 8-14)	Week 3 (Days 15-21)	Week 4 main dose (Days 22-28) to Week 8 main dose (Days 50-56)
Low dose				
≥40	12	24	30	36
≥40, CYP impaired	6	12	18	18
30 to <40	6	12	18	24
30 to <40, CYP impaired	6	12	12	12
20 to <30	6	12	18	18
20 to <30, CYP impaired	6	6	6	6
High dose				
≥40	12	24	36	48
≥40, CYP impaired	6	15	24	30
30 to <40	12	24	30	36
30 to <40, CYP impaired	6	12	18	18
20 to <30	12	18	24	30
20 to <30, CYP impaired	6	12	12	12

CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer.

3.9. Study Procedures and Flowchart

Study procedures and assessments with their time points are presented in Table 2. During a visit, study procedures and assessments should be performed in the order specified in the study manual.

Table 2: Study Procedures and Assessments

	Pre-screening	Screening	BL[a]	Escalation period (weeks)			Maintenance period (weeks)				Follow-up (weeks)		Unsche-duled
Study week[b]	**Up to 3 months**	**Up to 31 days**	**Day 1**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**6 (Day 42)**	**7 (Day 49)**	**8/ ET[c] (Day 56)**	**9 (Day 63)**	**10[d] (Day 70)**	
Visit window (days)			**0**	**±3 days**							**±3 days from week 8**		
Informed consent/assent	X	X											
Randomization			X										
Clinic visit		X[e]	X		X		X			X	X		X
Telephone contact				X		X		X	X			X	
Dose escalation[f]				X	X	X							X[g]
Eligibility criteria		X	X										
Medical and psychiatric history		X											
Demographics		X											
Vital signs and weight[h]		X	X[i]		X		X[i]			X[i]	X		X
Physical examination		X								X			X[j]
Neurological examination		X								X			X[j]
Height		X								X			
12-Lead ECG[k]		X	X				X			X			X[j]
PK blood sampling										X[l]			

	Pre-screening	Screening	BL[a]	Escalation period (weeks)			Maintenance period (weeks)				Follow-up (weeks)		Unsche-duled
Study week[b]	**Up to 3 months**	**Up to 31 days**	**Day 1**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**6 (Day 42)**	**7 (Day 49)**	**8/ ET[c] (Day 56)**	**9 (Day 63)**	**10[d] (Day 70)**	
Visit window (days)			**0**	**±3 days**							**±3 days from week 8**		
Chemistry/hematology/ urinalysis		X								X			X[j]
Urine drug screen		X								X			X[j]
CYP2D6 genotype[m]		X											
β-HCG test[n]		X	X				X			X			X[j]
MINI Kid[o]		X											
CDI-2 (Parent and Self-report versions)[p]		X	X		X		X			X	X		X[j]
C-SSRS (Children's Baseline/Screening)[q]		X											
C-SSRS (Children's Since Last Visit) [q]			X		X		X			X	X		X[j]
YGTSS[r s]		X	X		X[t]		X			X	X[t]		
TS-CGI[s]			X		X		X			X	X		
TS-PGII[s]			X		X		X			X	X		
[redacted]			X		X		X			X	X		
[redacted]			X		X		X			X	X		
[redacted]			X				X[u]			X	X[u]		

	Pre-screening	Screening	BL[a]	Escalation period (weeks)			Maintenance period (weeks)				Follow-up (weeks)		Unsche-duled
Study week[b]	**Up to 3 months**	**Up to 31 days**	**Day 1**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**6 (Day 42)**	**7 (Day 49)**	**8/ ET[c] (Day 56)**	**9 (Day 63)**	**10[d] (Day 70)**	
Visit window (days)			**0**	**±3 days**							**±3 days from week 8**		
C&A-GTS-QOL[q]			X				X			X			X[j]
Dispense IMP[v]			X		X		X						X[j]
Collect IMP					X		X			X			X[j]
Assess IMP accountability/compliance/ supply				X[w]	X	X[w]	X	X[w]	X[w]	X			X[j]
Assess AEs		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X

[a] The baseline visit (day 1) will occur the same day as the scheduled first dose of the IMP (day 1).
[b] Assessment will be performed at the end of study week (±3 days).
[c] For patients who withdraw prematurely, an early termination visit should be conducted as soon as possible after the last dose of IMP. In addition, 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 10.
[d] This visit is a telephone contact for safety evaluation, required only for patients who will not roll over into the open-label safety extension study for TEV-50717.
[e] The screening visit may be conducted over 2 separate visits at the discretion of the investigator.
[f] Patients will be provided with a diary to record critical information on dosing. The date and time of the last dose of study medication before the week 8 visit should be recorded in the diary by the patient or parent/legal guardian. The site will document the date and time of the sample collection. Prior to the clinic visit on week 8, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary.
[g] Dose escalation will only occur during the dose escalation period (i.e., from week 1 to week 3).
[h] Weight must be measured with shoes and outerwear off.
[i] Orthostatic blood pressure and pulse will be measured after patient is in standing position for at least 3 minutes.
[j] Assessment will be completed at investigator's discretion.
[k] All ECGs will be performed after at least 5 minutes of rest in a supine or semi-supine position.
[l] Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected within 2 to 3 hours after the first PK sample collection. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their IMP dose in the clinic after the first PK sample is collected.

[m] The patient's genotype for CYP2D6 will be blinded during the conduct of the study, except for the sample analysis and IRT vendor.
[n] For females who are postmenarchal or ≥12 years of age, a urine test will be administered at baseline and at week 4, while a serum test will be administered at screening, week 8, and if clinically indicated.
[o] MINI Kid (children and adolescents) modules to be used are Major Depressive Episode (Module A), (Hypo) Manic Episode (Module D), OCD (Module J), Alcohol Dependence/Abuse (Module L), Substance Dependence/Abuse (Non-alcohol; Module M), ADHD (Module O), Conduct Disorder (Module P), and Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).
[p] Children 6 years of age at baseline will not complete the self-report version; the parent/legal guardian will complete the parent version.
[q] For children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.
[r] Input from the caregiver/adult is required.
[s] The YGTSS, TS-CGI, TS-PGII, and TS-PGIS questionnaires should be performed before any blood draws or ECG assessments.
[t] 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).
[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 during escalation. See Table 1 for baseline weight-based dosing titration. At week 4, patients will receive doses for 4 weeks of treatment.
[w] The site needs to discuss the drug status during the telephone contacts to ensure that the patient has adequate tablets, inform the patient if they should escalate, and remind them to bring completed blister packs to the next in-clinic visit.

Abbreviations: AE=adverse event; ADHD=Attention Deficit Hyperactivity Disorder; β-HCG=beta human chorionic gonadotropin; BL=baseline visit; CDI-2=Children's Depression Inventory Second Edition; C-SSRS=Columbia Suicide Severity Rating Scale; [redacted] 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- scale; IMP=Investigational Medicinal Product; IRT=Interactive Response Technology; MINI Kid=Mini International Neuropsychiatric Interview For Children and Adolescents; OCD=obsessive-compulsive disorder; PK=pharmacokinetic; TS-CGI=Tourette Syndrome-Clinical Global Impression; TS-PGII=Tourette Syndrome-Patient Global Impression of Impact; [redacted]; YGTSS=Yale Global Tic Severity Scale.

4. Endpoints

4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients.

4.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

1. Change in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients;
2. Change in the TTS of YGTSS from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients;
3. Change in the TS-CGI score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients;
4. Change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients;
5. Change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients;
6. Change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS QOL) activities of daily living (ADL) subscale score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients;
7. Change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients.

4.3. Exploratory Endpoints

Exploratory endpoints are as follows:

[redacted]

[redacted]

4.4. Pharmacokinetic Endpoints

The pharmacokinetics of the alpha dihydrotetrabenazine (α HTBZ) and beta dihydrotetrabenazine (β HTBZ) metabolites of TEV-50717, and other metabolites (as needed), will be explored based on sparse sampling at Week 8.

4.5. Safety Endpoints

The safety endpoints for this study are as follows:

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

5. Analysis Sets

5.1. Screened Analysis Set

The screened analysis set will include all patients who are screened and have informed consent. This set will be used for patient listing and summary of patient disposition.

5.2. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients, regardless of whether or not a patient took any IMP. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

The ITT analysis set will be used for all study population summaries, unless otherwise noted. Summaries will be presented by treatment group and for all patients. Patients listing on efficacy data will be based on ITT analysis set.

5.3. Safety Analysis Set

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

All safety analyses and listings will be based on the safety analysis set.

5.4. Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set will include a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP and who have both a baseline and at least 1 post-baseline YGTSS assessment. In the mITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

All efficacy analyses will be based on the mITT analysis set.

5.5. Per-Protocol Analysis Set

The per-protocol (PP) analysis set will include patients who are compliant with study medication (80% to 105%), have a YGTSS assessment at baseline and at weeks 2, 4, and 8, and who have not taken prohibited concomitant medications as indicated in exclusion criterion, and who have no major protocol deviations that affect the validity of the efficacy measurements. Protocol deviations will be captured during the study conduct. Protocol deviations will be classified as major or minor prior to database lock. The list of protocol deviations will be reviewed before unblinding and major protocol deviations that could affect the primary and secondary variables will be determined. All exclusion from PP analysis set will be reviewed in the blinded data review meeting (BDRM) before database lock.

5.6. Major Protocol Deviations Results in Exclusion from Analysis Set

Some of the examples of major deviations that may result in patient or visit exclusion from any analysis set are given in Table 3.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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 9.3 or above.

Tables, listings and figures (TLFs) will be produced in accordance with the principles outlined by the ICH E3 guidelines. For most summary statistics, data will be analyzed by the following treatment groups: TEV-50717 High-Dose; TEV-50717 Low-Dose; Placebo. Total column will be included in all non-efficacy tables.

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.

6.2. Key Definitions

6.2.1. Baseline Values

Baseline is defined as the last non-missing measurement on or prior to the first dose of double-blind IMP.

6.2.2. First Dose Date

The first dose date will be the date that the first dose of randomized, double-blind IMP is administered. Dose starting and stopping dates are collected on CRF per blister per week. The first dose date will be derived as the earliest date obtained from CRF.

6.2.3. Last Dose Date

Last dose date is defined as the last dose stopping date. It will be derived as the latest dose stopping date obtained from CRF.

6.2.4. Study Day

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

6.2.5. Duration

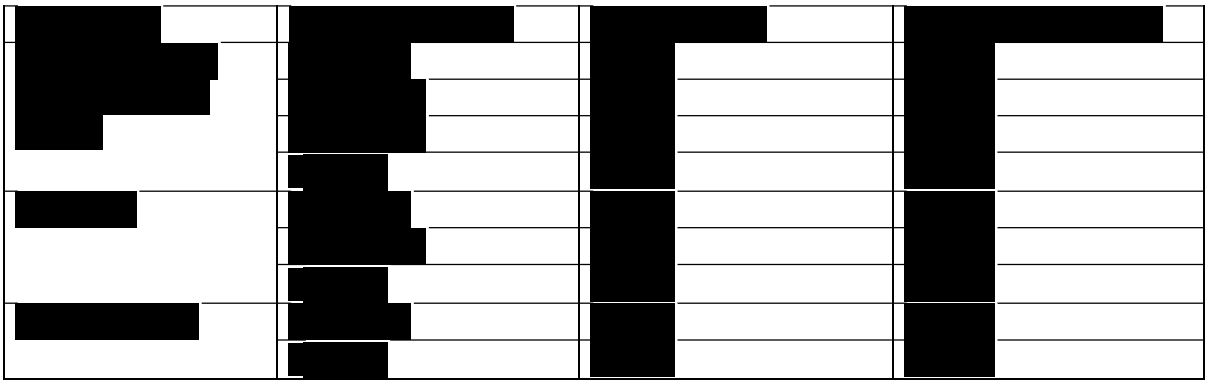
Duration of double-blind treatment will be determined as:
Duration = last dose date - first dose date + 1.

6.3. Missing Data

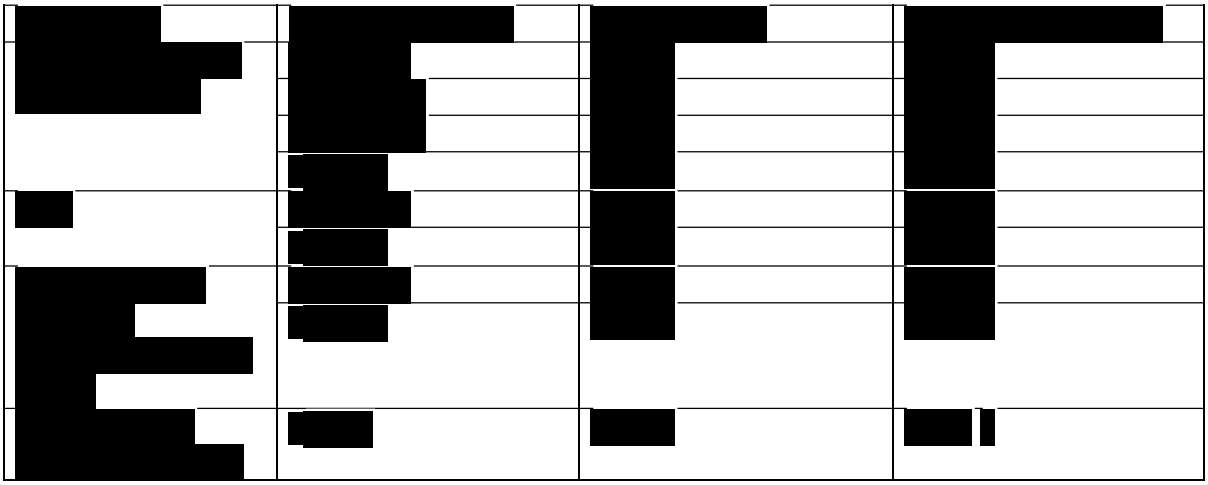
The handling of missing or incomplete data is described for each endpoint and data type (as needed) in Sections 8 to 9. In general, no data imputation will be applied for missing values in safety analysis. Data imputation method for efficacy analysis will be described in Section 8.

6.4. Visit Windows

[redacted]



[redacted]



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 scheduled visit in the analysis window, scheduled visit will be selected.
- If there is no scheduled visit, but early termination visit, early termination visit will be selected.
- If there are no scheduled or early termination visits, the unscheduled visit will be selected. If there are multiple unscheduled visits, the following rules will be used in sequential order:
    - The record closest to the planned assessment day will be selected for analysis.

- If 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.

For these analyses performed by time period, e.g. adverse events, the following definitions will be used:

- Escalation Period - from the first dose of treatment until the day before the week 4 visit. For patients discontinued before the week 4 visit, the Escalation Period is until the later of the last dose of treatment and the early termination visit.
- Maintenance Period - from the day of the week 4 visit until the day of the week 8 visit. If a patient enters the Maintenance Period but discontinues treatment early, the Maintenance Period is until the later of the last dose of treatment and the early termination visit.
- Follow-up Period - from the end of the Maintenance Period through the end of the study.
- Overall Period - includes the Escalation Period, the Maintenance Periods, and the Follow-up Period, if applicable.

If the AE onset date is partial and can be potentially counted in multiple periods, AE will be included with the earliest period.

6.5. Pooling of Centres

Patients will not be pooled based on site size, but rather by region, to ensure a sufficient number of patients per treatment arm in the ITT, mITT and PP sets for analysis that contain region as a model effect. The tables below show which countries comprise each of the regions to be used in analysis.

Region	Country
Europe	France
	Hungary
	Italy
	Netherland
	Poland
	Romania
	Sweden
	Ukraine
North America	United States
	Canada
Latin America	Argentina
	Columbia
	Mexico
Asia Pacific	Australia
	Korea

7. Demographic, Other Baseline Characteristics and Prior Medications

7.1. Patient Disposition and Withdrawals

Patient screened and patients screened but not in the ITT analysis set will be summarized only for all patients in screened analysis set using patient counts. Patients in the ITT analysis set, patients in the ITT analysis set but not treated, patients in safety, mITT, and PP analysis sets, patients who complete titration period, complete maintenance period, complete the study, complete the follow-up, and patients who withdraw from the study (and reason for withdrawing) during each treatment period will be summarized using descriptive statistics. The ITT analysis set will be used as the denominator for calculating percentages.

If more than 15% of the patients withdraw from the study during the treatment period, the number of days until study discontinuation will be plotted using Kaplan-Meier methodology using the ITT analysis set (defined in section 5.3). Patients who complete the study treatment period will be censored on the study day of the last dose.

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

In addition, the major protocol deviations will be summarized for ITT analysis set.

7.2. Demographic and Other Baseline Characteristics

Patient demographics and baseline characteristics will be examined to assess the comparability of the treatment groups. BMI will be computed as:

BMI (kg/m^2) = Weight at baseline (kg)/[Height at screening $(m)^2$].

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).

The continuous variables of patient age, weight, height, body mass index (BMI), BMI World Health Organization (WHO) adjusted z-scores and percentile, will be summarized using descriptive statistics. The categorical variables of patient sex, race, ethnicity, and BMI categories will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary. For randomized patients, age at baseline will be used.

The continuous variables of time since Tourette syndrome diagnosis in years and baseline TTS of the YGTSS will be summarized using descriptive statistics. The categorical variables of age group at baseline (6 to 11 years, 12 to 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) will be summarized using descriptive statistics for each category.

Strong CYP2D6 inhibitor status is determined by classifying patients as taking versus not taking a strong CYP2D6 inhibitor (i.e. paroxetine, fluoxetine, or bupropion), collected at screening from site. Impaired CYP2D6 function is defined as use of a strong CYP2D6 inhibitor at baseline or a poor CYP2D6 metabolizer. Both CYP2D6 genotype and impairment status will be blinded during the study.

Summaries for demographics and baseline characteristics will also be presented for the ITT, safety, mITT and PP analysis sets.

7.3. Medical History and Concomitant Diseases

Significant 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. Significant surgical 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 by treatment group, system organ class (SOC), and MedDRA preferred term (PT). Patient data will be listed.

7.4. Medication

Any prior therapy, medication, or procedure a patient has had within 3 months before study drug administration will be recorded on the case report form (CRF). 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, by treatment group, 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 and therapies stopped before the first day of study drug administration. Prior medication will be summarized by the ATC level 3 and preferred name. Prior medication will be summarized. The 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 CRF. Type of treatment/procedure and indication will be listed.

Prior treatment given for TS will be summarized. The 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. If the start date is partial with year and month, 1st will be imputed. If the start date has only year, Jan, 1st will be imputed. If the end date is partial, the latest possible date on or before informed consent date will be imputed. If there are multiple prior treatments, the duration will be computed as the sum of all non-overlapping treatments. For overlapping treatments, the duration will be from the earliest treatment start date to the latest treatment end date.

8. Efficacy

The mITT analysis set will be used for all efficacy analyses, unless otherwise noted. Analyses and summaries will be presented by treatment group.

Week 9 efficacy data will be summarized but will not be included in any statistical analyses.

8.1. Efficacy Assessment and Time Points

8.1.1. Yale Global Tic Severity Scale (YGTSS)

The YGTSS rating scale is a semi-structured clinician rating instrument that provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic tics (Leckman et al 1989). The YGTSS is composed of 11 items: 5 items for motor tic severity, 5 items for vocal tic severity, and 1 item for impairment. Each item for motor tic severity and vocal is rated on a 6-point scale (0 for none to 5 to severe). The MTSS is the sum of the 5 items for motor tic severity and the VTSS is the sum of the 5 items for vocal tic severity. The TTS is the sum of the MTSS and the VTSS. The impairment score ranges from 0 (none) to 50 (severe). The GSS is the sum of the TTS and the impairment score.

YGTSS is administered at screening; baseline; and weeks 2, 4, 8, and 9.

For YGTSS, if a response to 1 item is missing within the MTSS or VTSS subscale, the missing response will be replaced with the average of the remaining responses within the subscale; if responses to 2 or more items within a subscale are missing, the missing responses will not be replaced and the subscale score will be set to missing; if at least 1 subscale is missing then the TTS will be set to missing. If the TTS or impairment score are missing, then the GSS will be set to missing.

8.1.2. Tourette Syndrome-Clinical Global Impression (TS-CGI)

The TS-CGI is administered at baseline and at weeks 2, 4, 8, and 9. The TS-CGI scale is a 7-point Likert scale that allows the clinician to use all available information to assess the impact of tics on the patient's quality of life. The TS-CGI is rated as follows: 1 (normal), 2 (borderline), 3 (mild), 4 (moderate), 5 (marked), 6 (severe), and 7 (extreme).

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

The TS-PGII is administered at baseline and weeks 2, 4, 8, and 9. 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. Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS QOL)

The C&A-GTS-QOL is administered at baseline, week 4, and week 8. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

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

- Cognitive (questions 11, 12, 13, 14, 18, 20, 21, 23) (range: 0- 32)
- Psychological (questions 15, 16, 17, 19, 25, 27) (range: 0 – 24)
- Obsessive-compulsive (questions 7, 8, 9, 10) (range: 0 – 16)
- Physical (questions 1, 3, 4) (range: 0 – 12)
- Coprophenomena (questions 5, 6, 22) (range: 0 -12)
- ADL (questions 2, 24, 26) (range: 0-12)

Scores for the six subscales are generated by summing items and, for ease of interpretation, transformation to a range of 0 to 100 (100x [(observed score - min possible score)/(max possible score - min possible score)]). The total score, resulting from the sum of the subscale scores, is also normalized to a 0–100 range. For C&A-GTS-QOL, if a response to 1 question is missing within the subscale, the missing response will be replaced with the average of the remaining responses within the subscale; if responses to 2 or more questions within a subscale are missing, the missing responses will not be replaced and the subscale score will be set to missing; if at least 1 subscale is missing then the total score will be set to missing. For all analysis and summary, transformed scores will be used.

8.1.5. [redacted]

[redacted]

8.1.6. [redacted]

[redacted]

8.2. Primary Efficacy Endpoint and Analysis

8.2.1. Primary Efficacy Analysis

The primary analysis will be a mixed-model, repeated-measures with the change in the TTS as the dependent variable. The model will include fixed effects for treatment group, week (3 levels: weeks 2, 4, and 8), and the treatment group by week interaction. The baseline TTS, region, and age group at baseline (2 levels: 6-11 year, 12-16 years) will be included as covariates. The unstructured covariance matrix for repeated observations within patients will be used. In case that the model does not converge, the Maximum-Likelihood estimation method will be used instead of the default Restricted Maximum-Likelihood. If the model still does not converge, then a simpler covariance structure with fewer parameters will be used, according to the following order: Heterogeneous Autoregressive (1), Heterogeneous Compound Symmetry, Autoregressive (1), and Compound Symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The least squares means of the change in TTS from baseline at week 8 will be compared (primary: TEV-50717 high-dose arm vs. the placebo arm; secondary: TEV-50717 low-dose arm vs. the placebo arm) using 2-sided tests at the alpha=0.05 level of significance. The SAS code for this test is as follows:

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 each comparison (TEV-50717 high-dose vs. placebo at week 8; TEV-50717 low-dose vs. placebo at week 8) will be presented.

Cohen's d effect size will also be computed for each comparison (Kelley, 2007). Cohen's d is calculated as:

$$d = (\mu t - \mu p) / (\text{pooled SD}),$$

where μt represents the least-square (LS) mean of the specified TEV-50717 group (High- or Low-dose, μp is the LS mean of the placebo group, and the pooled SD is based on the adjusted LS means and adjusted standard errors from the mixed-effect model for MMRM, specifically:

$$Pooled\ SD = \frac{Standard\ Error\ (SE)}{\sqrt{\frac{1}{nt} + \frac{1}{np}}}$$

and nt=number of patients in specified TEV-50717 group and np=number of patients in placebo group.

The utility of Cohen's d is to help judge the clinical importance of a measured treatment difference.

8.2.2. Sensitivity Analysis

The primary efficacy analysis on change in the TTS at Week 8 is to use MMRM model, described in Section 8.2.1 (the primary analysis model), using all observed data in the mITT anlaysis set. Data from patients that had dose reduction, suspension, treatment discontinuation, or treatment-related adverse events were collected in the study and will be included in the analyses, as these patients are generally

not excluded from the mITT analysis set. This model is appropriate when data isMAR. This approach is considered reasonable under the assumption that the percent of early terminations will be low. As of 12 Dec 2019 the overall early termination rate from study 30060 was 8%, which is regarded to be in line with this assumption. Therefore, the proposed analysis is suitable for the primary estimand.

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

[redacted]

Details of sensitivity analysis for missing data and the statistical model are explained in the next 2 sections.

8.2.2.1. Sensitivity analyses for missing data

[redacted]

[redacted]

[redacted]

The complete multiple imputation methodology, along with SAS code, is detailed in Appendix C (Section 19.3).

8.2.2.2. Sensitivity analysis for the statistical model

[redacted]

8.2.3. Subgroup Analysis

Data summary of TSS of YGTSS by subgroup below will be conducted using the mITT population. In addition, 95% CI for the change from baseline will be provided:

- Gender: Male and Female
- Race Group: White, Black or African American, and Other
- Baseline Age Group (6-11 years, 12-16 years)
- CYP2D6 impairment status (Yes/No)

In addition, TTS of YGTSS will be analyzed in the same fashion as the primary analysis in Section 8.2.1 by baseline age group, with the exception that age group will not be included as the fixed effect.

8.3. Secondary Efficacy Endpoint(s) and Analyses

The secondary endpoints for this study are as follows:

1. Change in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients;
2. Change in the TTS of YGTSS from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients;
3. Change in the TS-CGI score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients;
4. Change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients;
5. Change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients;
6. Change in the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life (C&A-GTS QOL) activities of daily living (ADL) subscale score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients;

7. Change in the C&A-GTS-QOL ADL subscale from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients.

A hierarchical (fixed-sequence) testing approach will be used for the analysis of the primary and key secondary endpoints to maintain the experiment-wise type I error rate of 5%. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory.

Secondary efficacy analyses will be based on mITT analysis set.

8.3.1. Secondary Efficacy Analysis

8.3.1.1. Analysis of the change in the TS-CGI from baseline to Week 8

The change in the TS-CGI score from baseline to Week 8 (1st and 3rd secondary endpoints) will be analyzed in the same fashion as the primary analysis in Section 8.2.1, with the exception that the baseline value of the given endpoint will be included as the covariate.

8.3.1.2. Analysis of the change in the TTS of YGTSS between low-dose TEV-50717-treated patients and placebo-treated patients

The change in the TTS of YGTSS from baseline to Week 8 between low-dose TEV-50717 treated patients and placebo-treated patients (2nd secondary endpoint) will be analyzed as part of Section 8.2.1.

8.3.1.3. Analysis of the change in TS-PGII

The change in the TS-PGII score from baseline to Week 8 (4th and 5th secondary endpoints) will be analyzed using a Cochran-Mantel-Haenszel (CMH) row mean score test with modified ridit scoring, controlling for baseline TS-PGII. The TS-PGII will be summarized as shifts from baseline score to each visit that it is measured using descriptive statistics.

The SAS code for the analysis at week 8 for each pair of high-dose TEV-50717 and placebo, or low-dose TEV-50717 and placebo is as follows:

[redacted]

8.3.1.4. Analysis of the change in C&A-GTS-QOL ADL subscale

The change in the C&A-GTS-QOL ADL subscale score from baseline to week 8 (6th and 7th secondary endpoints) will be analyzed in the same fashion as the primary analysis in Section 8.2.1, with the exception that the baseline value of the given endpoint will be included as the covariate.

8.3.2. Sensitivity Analysis

[redacted]

[redacted]

8.4. Exploratory Endpoints and Analysis

Exploratory endpoints for this study are as follows:

[redacted]

[redacted]

8.4.1. [redacted]

[redacted]

8.4.2. [redacted]

[redacted]

8.4.3. [redacted]

[redacted]

9. Safety

The safety endpoints for this study are as follows:

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

The safety analysis set will be used for all safety analyses. Summaries will be presented by treatment group and for all patients.

9.1. Extent of Exposure

Duration of exposure to study drug (days) for individual patients is the number of days patient received drug (last day of study drug – first day of study drug + 1). Duration of treatment (days) will be summarized using descriptive statistics. Weeks on treatment using the categories ≤2 weeks, >2 to ≤4 weeks, >4 to ≤6 weeks, >6 to ≤8 weeks, and >8 weeks will also be summarized using descriptive statistics.

9.2. Treatment Compliance

Study drug administration will be included in the CRF. In the form, med ID (ID for blister pack), week range, dosing start and stop date, and number of pills taken from the blister pack are collected. Treatment compliance (%) is calculated as 100*(total number of pills taken / number of tablets expected to be used). The total number of pills taken is the sum of pills taken from all bottles dispensed, identified by med ID. 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. The number of pills expected to be used is based on the number of morning and evening dosing times during the treatment period (2 pills are used for each dosing time point). A patient will be deemed compliant over the treatment period if the patient has taken 80% to 105% of the expected tablets of study drug.

Treatment compliance (%) will be summarized as continuous data using descriptive statistics. In addition, treatment compliance will be summarized as categorical data using descriptive statistics for the following categories: <80%, 80% to 105%, >105%.

9.3. Concomitant Medication

A concomitant medication is 1)any medication that starts prior to first day of study drug administration and continues into treatment period; or 2) any medication that starts on or after the first dose of IMP and before the last dose of IMP. Concomitant medication will be summarized separately for 1) and 2). In the

case of completely missing stop date and medication is not ongoing, medication will be assumed to be concomitant. Medication cannot be considered as both prior and 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, by treatment group, 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.

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

- Proportion of patients requiring new medication;
- Proportion of patients requiring increased medication;
- Proportion of patients requiring decreased medication;
- Proportion of patients discontinued medication;
- Proportion of patients with medication switch.

9.4. Adverse Events

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

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 or higher.

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 study drug interruption, and TEAEs leading to death. The overall summary will also be prepared by age group (6-11 years, or 12-16 years);
- 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 treatment-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 study drug 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 in either of the treatment groups. ;
- SMQs for suicide/self-injury, depression (exclude suicide and self-injury), and Parkinson-like events.

For summary tables, patients having more than 1 event with the same PT will be counted once for that term. Patients having more than 1 event with the same SOC will be counted once for each event and once for that SOC. 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. Summaries will be presented by treatment group and for all patients. The denominator for percentages will be the number of patients in safety analysis set for the given treatment group (i.e., the N's for the columns). Summary of all TEAEs will be presented in the overall period (escalation plus maintenance phase plus follow-up period) and for the escalation period, maintenance period, and follow-up period. By period summary will be based on the period the AE occurred (Section 6.4). Same type of AE may be counted in multiple periods in cases below:

- AE resolved in the same period and reoccurred in a new period.
- AE increased severity in another period.

Same AE will be counted only once in summary in the overall period.

All adverse events in the overall treatment period will be summarized by CYP2D6 impairment status (Impaired/Not impaired). In addition, serious AEs and AEs by severity will be summarized by CYP2D6 impairment status.

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

- All AEs
- Serious AEs
- AEs leading to study drug discontinuation
- AE leading to dose interruption
- AEs leading to death.

9.5. Laboratory Evaluations

Laboratory tests will include chemistry panel, hematology panel, and urinalysis testing. Laboratory tests will be performed at the following time points: at the screening visit, and at week 8. If clinically significant laboratory abnormalities have been noticed at week 8 visit, those laboratory evaluations will be repeated at the week 9 visit. A list of laboratory tests is included in Table 4.

Observed values (in SI units) and change from baseline to Week 8 will be summarized by treatment group. 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 Week 8 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 4: List of Laboratory Tests

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

9.6. Pregnancy

Pregnancy tests will be performed for females who are postmenarchal or ≥12 years of age. Urine test will be administered at baseline, and serum test will be administered at screening and Week 8. The pregnancy data will be presented in a data listing.

9.7. Urine Drug Screening

Urine drug screening tests are collected at screening and week 8. The urine drug screening data will be presented in a data listing.

9.8. Vital Signs

Vital signs will be measured at screening, baseline, and weeks 2, 4, 8, and 9. 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 baseline, weeks 4, and 8. BMI will be computed similarly as in Section 7.2 at Week 8 and early termination visits. Weight and height at the visit will be used. 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.

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 by treatment and overall.

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 treatment period according to criteria specified in Table 5. A listing will be provided for all markedly abnormal vital signs. A shift table for BMI age and sex adjusted categories will be presented comparing shifts from the baseline visit to week 8. Percentages will be based on the number of safety patients with a non-missing value for both the baseline and post-baseline visit for the given vital sign.

Table 5: 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.

9.9. ECG

Assessment of Standard 12-lead ECG are obtained at screening, baseline, weeks 4 and 8. A central ECG Standard 12-lead ECG will record heart rate (HR), PR interval, RR interval, QT interval, Frederica's corrected QT interval (QTcF), and QRS duration. The overall ECG assessment will be centrally reported as "Normal" or "Abnormal" with respect to relevant abnormalities. 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. If ECG tests are repeated on the same day for any other reason per investigators discretion, the average of all ECG values on that day will be used for summary.

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

In addition, for QTcF, average baseline confirmed QTcF (the average of the screening and Day 1 QTcF), and the change from average baseline will be summarized by treatment and overall, and by 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 treatment and overall, and by visit.

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

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

Criteria for abnormal values used in the study are presented in Table 6.

Table 6: 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

9.10. Physical Examinations

Physical examinations are performed obtained at screening and Week 8. Physical examinations will not be summarized. Physical examinations will be listed.

9.11. Neurological Examinations

Neurological examinations will be performed at screening and Week 8. Each assessment (i.e. Mental Status, Cranial Nerves, Motor System, Gait and Balance, Tendon Reflexes, Sensation and Other) will include category of normal/abnormal and not clinical significant (NCS)/abnormal and clinical significant (CS). Neurological examinations will be listed.

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:

[redacted]

[redacted]

Summary statistics will be provided to the observed values and change from baseline. This analyses are only exploratory and for signal detection purpose.

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

The CDI-2 (parent and self-report versions) is administered at screening, baseline, and weeks 2, 4, 8, and 9. 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, 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 CDI-2 parent version and self-report versions subscale scores, raw scores, and self-report version T scores will be presented at baseline and each visit each is measured.

9.14. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS children's baseline/screening scale assesses past and current suicidal ideation and behaviors to determine suicide risk and is administered at screening. The C-SSRS children's since last visit (SLV) scale is administered at baseline and at weeks 2, 4, 8, and 9. 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 (1) Wish to be Dead – if response to Question 1 is Yes and responses to Questions 2-5 are No. (2) Non-Specific Active Suicidal Thoughts – if response to Question 2 is Yes and response to Questions 3-5 are No. (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. (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. (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 (7) Aborted Attempt – if response to Aborted Attempt is Yes and responses to Actual Attempt, Aborted Attempt, and Completed Suicide are No. (8) Interrupted Attempt – if response to Interrupted Attempt is Yes and response to Aborted Attempt, and Completed Suicide are No. (9) Actual Attempt – if response to Actual Attempt is Yes and Completed Suicide is No. (10) Completed Suicide - if response to Completed Suicide is Yes (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 will be summarized by treatment and overall, and visit. For baseline/screening version at baseline, past 2 years scores will be summarized.

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 during the treatment period, by treatment and overall.

10. Pharmacokinetic Analysis

Samples collected for PK analysis will be quantified for α-HTBZ and β-HTBZ of TEV-50717, and other metabolites (as required), may be analyzed using population PK techniques. Analysis methods will be detailed in a separate exploratory population PK analysis plan.

11. Interim Analyses

No interim analysis is planned.

12. Changes from Analysis Planned in Protocol

A new exploratory endpoint is added:

- [redacted]

13. Reference List

Heitjan DF and Little RJA. Multiple Imputation for the Fatal Accident Reporting System. Applied Statistics 1991; 40:13–29.

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Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WL, et al. Children's Yal-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry 1997;36(6):844-52.

Ratitch B, Lipkovich I, O'Kelly M. Combining Analysis Results from Multiply Imputed Categorical Data. PharmaSUG 2013 – Paper SP 03

14. Programming Considerations

[redacted]

14.1. [redacted]

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14.2. [redacted]

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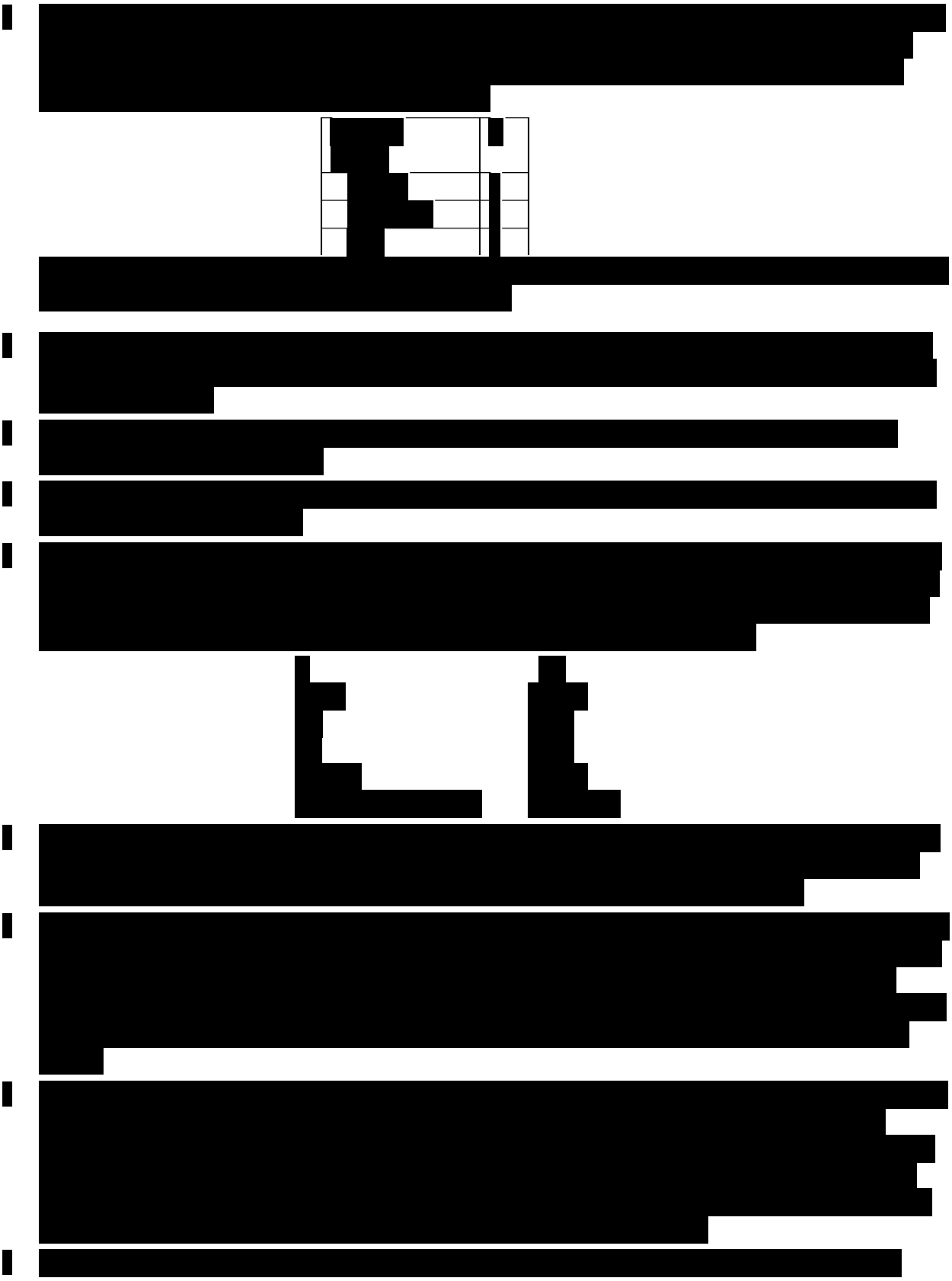

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14.2.6. [redacted]

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15. 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.

16. Index of Tables

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19. Appendices

[redacted]

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19.2. [redacted]

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19.3. [redacted]

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19.4. [redacted]

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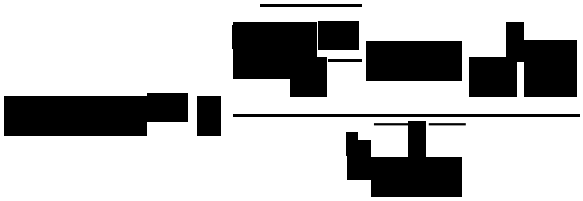

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