Statistical Analysis Plan

A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

Study Number TV50717-CNS-30046

NCT03452943

SAP Approval Date: 02-Dec-2019

Statistical Analysis Plan

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

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0.1	28-Feb-2018	[redacted]	Initial Release Version
0.2	05-Apr-2018	[redacted]	Update per sponsor comments
1.0	02-May-2018	[redacted]	Update per sponsor comments
1.1	31-May-2018	[redacted]	• Date the version based on the date of the last signature. • The header notes to Version 1.1 • On page 49 there is text that states: "Error! Reference source not found" • On page 75 remove headings for Mock ups • Bookmark revision history and signature page • Make all table title format consistent
2.0	19-Jun-2018	[redacted]	Change Version 1.1 to 2.0 for sign off
2.1	20-May-2019	[redacted]	[redacted] • Other updates include: o Correct TOC for minor errors; o In Section 9.9, ECG clinical significance is removed, as it is not collected in clinical database; o In Section 9.9, "Markedly Abnormal" is changed to "Abnormal", as there is no defined "Markedly" abnormal; o In Section 9.4, TEAE leading to dose reduction and SMQs for suicide/self-injury and depression (exclude suicide and self-injury) are added to Section 9.4; o ADHD and antidepressant prior medication and medication shift are added; o ADHD symptom over time is summarized; o Type of PD is updated to be consistent with actual PD reported. o To include derivation rule when ECG tests are repeated due to reason other than meeting QTcF criterion. o Update prior non-pharmacological treatment analysis method from by SOC/PT, as they are not coded.

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
3.0	10-Jul-2019	[redacted]	• Update per comments [redacted] • Correct typographical errors in Section 2.2 [redacted] • Correct typographical errors in header for Section 5.6 • Clarification/specification of time points in Section 8.3.4
3.1	26-Nov-2019	[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; [redacted] • 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; [redacted] • Index of tables, listings, figures are corrected.
4.0	02-Dec-2019	[redacted]	[redacted]

APPROVALS

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

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LIST OF TABLES

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

Abbreviation	Description
GCP	Good Clinical Practice
GPSP	Global Subject Safety and Pharmacovigilance
GSS	Global Severity Score
HD	Huntington disease
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

Abbreviation	Description
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
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
TD	Tardive Dyskinesia
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

INC Research 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 13 follow-up visit and enter the open-label safety extension study TV50717-CNS-30047, or complete week 14 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 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 efficacy of TEV-50717 to reduce motor and phonic tics associated with Tourette syndrome (TS).

3.2. SECONDARY OBJECTIVE

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

3.3. BRIEF DESCRIPTION

This is a Phase 2/3, randomized, double-blind, placebo-controlled, parallel group study in which patients with tics associated with TS will be invited to participate. Patients who qualify for the study will be centrally randomized in a 1:1 ratio (stratified by age at baseline [6 to 11 years, 12 to 16 years]) to receive either TEV-50717 or placebo. Throughout the study, patients will interact regularly with investigative site personnel, in clinic and by telephone, for the evaluation of safety, tic severity, and behavioral status (in clinic only). The target dose for each patient receiving TEV-50717 will be based on body weight and cytochrome P450 2D6 (CYP2D6) impairment status at baseline. Patients will be classified as CYP2D6 impaired if they are receiving a strong CYP2D6 inhibitor or are a CYP2D6 poor metabolizer based on blinded assessment of CYP2D6 genotype at baseline. CYP2D6 status will be used by Interactive Response Technology (IRT) for randomization into the study. The dose of investigational medicinal product (IMP) for each patient will be titrated to an optimal level followed by maintenance therapy at that dose. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers pre-specified by the IRT (Table 1). The overall treatment period will be 12 weeks in duration, including a titration period of 7 weeks, a maintenance period of 5 weeks, followed by a washout period of 1 week.

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

3.4. PATIENT SELECTION

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 exclusion criteria.

3.5. DETERMINATION OF SAMPLE SIZE

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

3.6. TREATMENT ASSIGNMENT & BLINDING

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

3.6.1. 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 INC Research.

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

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

3.6.2. Blinding

Patient randomization codes will be maintained in a secure location within INC Research, Biometrics. At the time of analysis, when treatment codes are needed, the INC Research 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 (ie, 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.

INC SOP 03.005.01 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.

In the event of accidental unblinding, the process described by INC Research SOP 28.004 (Management of Unblinding Scenarios) will be followed. As a minimum, each accidental unblinding occurrence will be escalated to the project lead who will work with the functional lead to investigate how/why the blind was compromised, determine whether to remove any of the accidentally unblinded personnel from the project, and ensure the required documentation and additional communication is in place.

3.7. ADMINISTRATION OF STUDY MEDICATION

Investigational medicinal product (TEV50717 or Placebo) will be dispensed in the clinic. Patients will receive doses for 2 weeks at baseline, week 2, and week 4 visits (current dose level and next dose level) to cover the telephone contacts. At week 6 and week 9 visits, patients will receive doses for 3 weeks.

IMP will be administered as follows:

- IMP should be swallowed whole and taken with food. Tablets should be taken with food (eg, 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.
- The starting dose is 6 mg in all patients. Daily doses will be administered twice daily, approximately 8 to 10 hours apart during the day. A minimum of 6 hours should elapse between doses. If a patient misses a dose and it is within 6 hours of their next dose, the missed dose should be skipped.
- After week 1, dose increases may not occur more frequently than every 5 days.
- 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 titration period, the dose of the IMP will be adjusted weekly according to Table 1 to identify a dose level that optimally reduces tics and is well tolerated. Investigators will be blinded to CYP status, with a dose cap for poor metabolizers pre-specified by the IRT.

Table 1: Maximum Daily Dose of IMP by Study Day and Weight Category at Baseline

	Weight category					
Study day[a]	**20 to <30 kg**		**30 to <40 kg**		**≥40 kg**	
CYP impairment status	**Not impaired**	**Impaired**	**Not impaired**	**Impaired**	**Not impaired**	**Impaired**
Day 1-7	6 mg	6 mg	6 mg	6 mg	6 mg (Days 1 and 2) 12 mg[b]	6 mg (Days 1 and 2) 12 mg[b]
Day 8-14	12 mg	12 mg	12 mg	12 mg	18 mg	18 mg
Day 15-21	18 mg	18 mg	18 mg	18 mg	24 mg	24 mg
Day 22-28	18 mg	18 mg	24 mg	24 mg	30 mg	30 mg
Day 29-35	24 mg	18 mg	30 mg	24 mg	36 mg	36 mg
Day 36-42	24 mg	18 mg	36 mg	24 mg	42 mg	36 mg
Day 43-49	30 mg	18 mg	42 mg	24 mg	48 mg	36 mg

[a] Administration of a given dose will take place throughout the days indicated. The new dose starts the morning after the telephone contact or the morning after the clinic visit (ie, Days 8, 15, 22, 29, 36, and 43), as applicable.
[b] Patients will receive 6 mg on days 1 and 2, and 12 mg starting on day 3.
bid=twice a day; CYP=cytochrome P450; IMP=investigational medicinal product.
Note: CYP impaired patients are those patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer. The investigator, in consultation with the patient and caregiver/adult, will determine if a dose increase is warranted to achieve optimal tic reduction.

3.8. 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

	Screening	BL[a]	Titration							Maintenance		Follow-up		U
Study week[b]	**Up to 31 days**	**Day 1[c]**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**5 (Day 35)**	**6 (Day 42)**	**7 (Day 49)**	**9 (Day 63)**	**12/ET[d] (Day 84)**	**13 (Day 91**	**14[e] (Day 98)**	
Visit window (days)		**0**	**±3 days**									**±3 days from Week 12**		
In-clinic visit	X[f]	X		X		X		X		X	X	X		X
Telephone contact			X		X		X		X				X	
Evaluate/Adjust IMP			X[g]	X	X[g]	X	X[g]	X	X					X
Informed consent/assent and/or co-consent for patients 14 years of age and older	X													
Eligibility criteria	X	X												
Medical history and psychiatric history	X													
Demographics	X													
Vital signs and weight[h]	X	X[i]		X		X[i]		X		X	X[i]	X		X
Physical examination	X										X			X[j]
Neurological examination	X										X			X[j]
Height	X										X			X[j]

	Screening	BL[a]	Titration							Maintenance		Follow-up		U
Study week[b]	**Up to 31 days**	**Day 1[c]**	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**5 (Day 35)**	**6 (Day 42)**	**7 (Day 49)**	**9 (Day 63)**	**12/ET[d] (Day 84)**	**13 (Day 91**	**14[e] (Day 98)**	
Visit window (days)		**0**	**±3 days**									**±3 days from Week 12**		
12-lead ECG[k]	X	X				X		X			X			X[j]
Pharmacokinetic blood sampling											X[l]			
Chemistry/Hematology/ Urinalysis	X										X	X[m]		X[j]
Urine drug screen	X										X			
Randomization		X												
CYP2D6 genotype[n]	X													
β-HCG test[o]	X	X				X					X			X[j]
MINI Kid[p,q]	X													
CDI-2 (Parent and Self-report)[r]	X	X		X		X		X		X	X	X		X[j]
C-SSRS (Children's Baseline/Screen)[q]	X													
C-SSRS (Children's Since Last Visit)[q]		X		X		X		X		X	X	X		X[j]
YGTSS[s,t]	X	X		X[u]		X		X[u]		X[u]	X	X[u]		

	Screening	BL[a]	Titration							Maintenance		Follow-up		U
Study week[b]	**Up to 31 days**	**Day 1**[c]	**1 (Day 7)**	**2 (Day 14)**	**3 (Day 21)**	**4 (Day 28)**	**5 (Day 35)**	**6 (Day 42)**	**7 (Day 49)**	**9 (Day 63)**	**12/ET**[d] **(Day 84)**	**13 (Day 91**	**14**[e] **(Day 98)**	
Visit window (days)		**0**	**±3 days**									**±3 days from Week 12**		
TS-CGI[t]		X		X		X		X		X	X	X		
TS-PGII[t]		X		X		X		X		X	X	X		
[redacted]		X		X		X		X		X	X	X		
[redacted]		X		X		X		X		X	X	X		
[redacted]		X						X[v]			X	X[v]		
C&A-GTS-QOL[q]		X						X			X			
Dispense IMP		X[w]		X[w]		X[w]		X[x]		X[x]				X[j]
Collect IMP				X		X		X		X	X			X[j]
Assess IMP accountability/compliance/supply			X[y]	X	X[y]	X	X[y]	X	X[y]	X	X			X[j]
Assess adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[z]	X	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]

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

[b] Assessment to occur at the end of the study week.

[c] Patients will be provided with a diary to record meal times and critical information on dosing. The date and time of the last dose of study medication before the week 12 visit should be recorded in the diary by the patient or caregiver/adult. The site will document the date and time of the sample collection. Prior to the clinic visit on week 12, patients will be reminded to record the start time of their last meal and the time of their last dose in their diary.

[d] For patients who withdraw prematurely, an early termination visit should be conducted as soon as possible after the last dose of IMP. All patients who discontinue early will have a follow-up telephone contact for safety evaluation 2 weeks after their last dose of IMP; evaluations will be as described for week 14 (Protocol Section 3.13.4.2).

[e] This visit is a telephone contact for safety evaluation, required only for patients who will not roll over into the open-label safety extension study TV50717-CNS-30047.

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

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

[h] Weight must be measured with shoes and outerwear off. Before pulse and BP are measured, the patient must be in a supine or semi-erect/seated position and resting for at least 5 minutes (the same position and arm should be used each time vital signs are measured for a given patient).

[i] Orthostatic BP and pulse will be measured after patient is in a standing position for at least 3 minutes.

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

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

[l] Two samples will be collected. The first sample will be collected upon arrival at the clinic. The second sample will be collected 2 to 3 hours after the first pharmacokinetic sample collection. Patients with early morning visits (ie, within 2 hours of their scheduled AM dosing) should take their IMP dose in clinic after the first pharmacokinetic sample is collected.

[m] Patients with clinically significant laboratory abnormalities at week 12 will have those laboratory evaluations repeated at the week 13 visit.

[n] The patient's genotype for CYP2D6 will be blinded during the conduct of the study.

[o] For females who are postmenarchal or ≥12 years of age, a urine test will be administered at baseline and week 4, while a serum test will be administered at screening and week 12, and if clinically indicated.

[p] MINI Kid (Children and Adolescents) modules to be used are: Major Depressive Episode (Module A), (Hypo) Manic Episode (Module D), OCD (Module J), Alcohol Dependence/Abuse (Module L), Substance Dependence/Abuse (Non-alcohol; Module M), ADHD (Module O), Conduct Disorder (Module P), and Psychotic Disorders and Mood Disorders with Psychotic Features (Module R).

[q] For children 13 years of age and under, interviews may be performed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

[r] Children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.

[s] Input from the caregiver/adult is required.

[t] The YGTSS, TS-CGI, TS-PGII, and TS-PGIS questionnaires should be performed before any blood draws or ECG assessments.

[u] Perform assessment of "Severity Ratings" of the questionnaire. Inventory portions, ie, "Motor Tic Symptom Checklist" and "Phonic Tic Symptom Checklist" do not need to be performed.

[v] Perform the Severity Ratings of OCD symptoms (Questions 1 through 10) only. Checklist does not need to be performed.

[w] IMP will be dispensed in the clinic; patients will receive doses for 2 weeks (current dose level and next dose level) to cover the telephone contacts. The site will determine titration (ie, starting the next dose) for the patient by telephone. See Table 1 for baseline weight-based dosing titration.

[x] Patients will receive doses for 3 weeks of treatment.

[y] 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, and remind them to bring used and unused IMP blister packs to the next in-clinic visit.

[z] Parents/Patients will be instructed during the course of the study to notify the investigator if any new medication is prescribed, including over-the-counter medications. Any prescribed medication should be reviewed with the investigator.

ADHD=Attention Deficit Hyperactivity Disorder; β-HCG=beta human chorionic gonadotropin; BL=baseline visit; BP=blood pressure; 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; IMP=investigational medicinal product; MINI Kid=Mini International Neuropsychiatric Interview For Children and Adolescents; OCD=obsessive-compulsive disorder; TS-CGI=Tourette Syndrome-Clinical Global Impression; TS-PGII=Tourette Syndrome-Patient Global Impression of Impact; [redacted] U=unscheduled visit; YGTSS=Yale Global Tic Severity Scale

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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 12

4.2. KEY SECONDARY EFFICACY ENDPOINTS

The key secondary efficacy endpoints are as follows:

1. Change in the Tourette Syndrome-Clinical Global Impression (TS-CGI) score from baseline to week 12
2. Change in the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII) score from baseline to week 12
3. 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 12

4.3. EXPLORATORY ENDPOINTS

Exploratory endpoints are as follows:

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 12.

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. 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 patients who receive at least 1 dose of IMP. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they were randomized. 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 all patients in the ITT population who receive at least 1 dose of IMP and have both a baseline and at least 1 post-baseline YGTSS assessment. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

All 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 week 9 or week 12, who have not taken prohibited concomitant medications as indicated in exclusion criterion, and 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 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 RESULTING 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]

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; Placebo.

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.

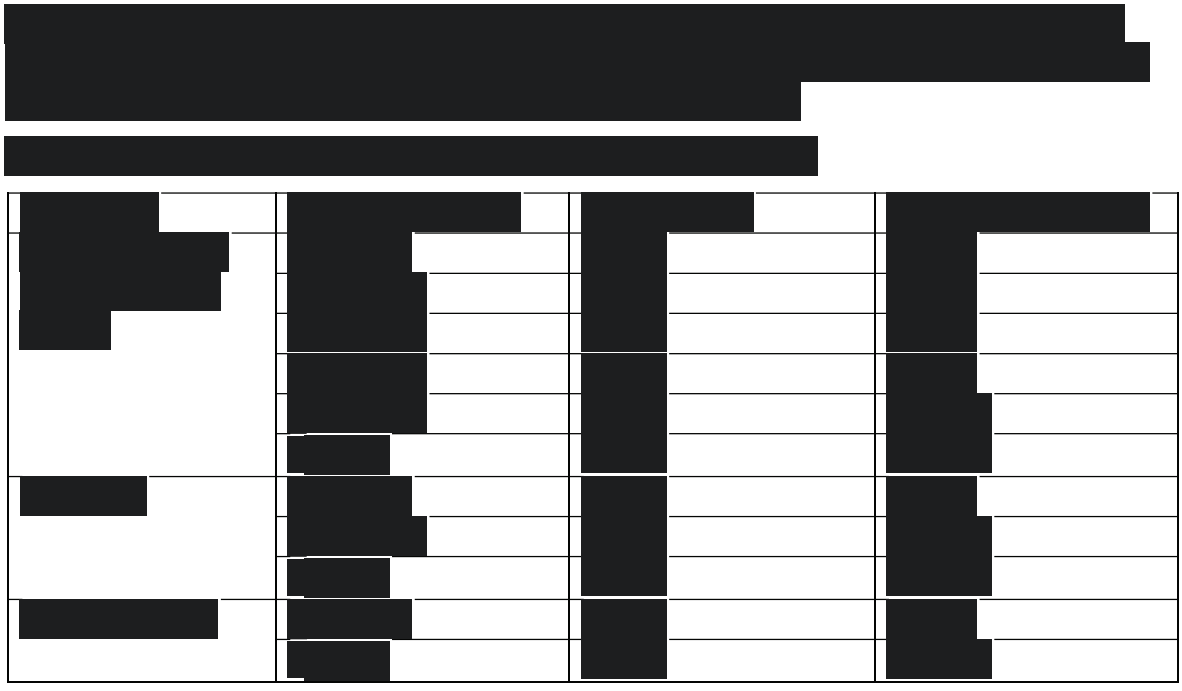
6.2.5. Duration

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

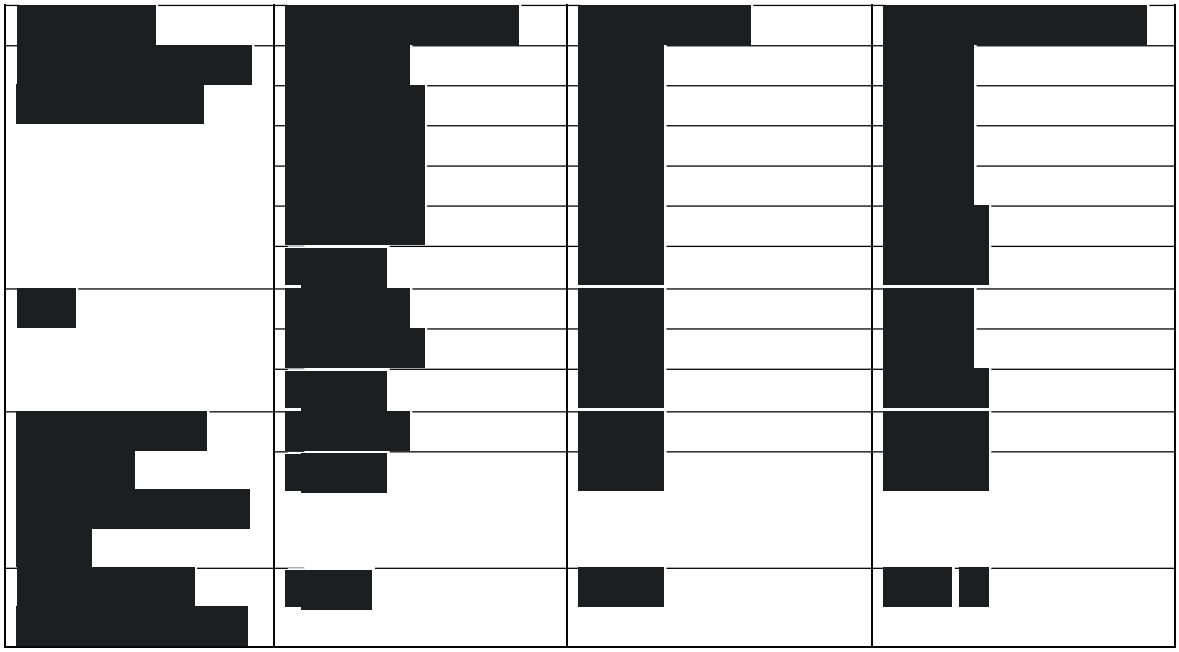
6.3. MISSING DATA

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]



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 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.

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

- Titration Period - from the first dose of treatment until the day before the week 7 telephone contact. For patients discontinued before the week 7 telephone contact, the Titration Period is until the later of the last dose of treatment and the early termination visit.

- Maintenance Period - from the day of the week 7 telephone contact until the day of the week 12 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 CENTERS

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
Euroasia	Denmark
	Spain
	Serbia
	Russia
North America	United States
	Canada

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, completed 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 before the end of the treatment period, the number of days until study discontinuation will be analyzed using Kaplan-Meier methodology using the ITT analysis set (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 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.

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 13 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, 6, 9, 12, and 13.

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, 6, 9, 12, and 13. 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, 6, 9, 12, and 13. 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 6, and week 12. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information.

The C&A-GTS-QOL is a 27-item questionnaire specific to TS patients that asks the patient to assess the extent to which their quality of life is impacted by their symptoms. The C&A-GTS-QOL contains 6 subscales (cognitive, coprophenomena, psychological, physical, obsessive-compulsive, and ADL) and uses a 5-point Likert scale ranging from no problem to extreme problem. Patients will also be asked how satisfied they feel overall with their life at that moment by using a VAS scale between 0 and 100 (Su et al 2017). 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 (5 levels: weeks 2, 4, 6, 9, and 12), and the treatment group by week interaction. The baseline TTS, region, and age group at baseline (2 levels: 6-11 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 12 will be compared (the TEV-50717 arm and the placebo arm) using a 2-sided test at the alpha=0.05 level of significance. The SAS code for this test is as follows:

[redacted]

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 at week 12) 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 TEV-50717 group, 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 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 12 is to use MMRM model, described in Section 8.2.1 (the primary analysis model), using all observed data. This model is appropriate when data is missing at random (MAR). To assess the robustness of the primary efficacy analysis, the following additional analyses will include:

[redacted]

[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]

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. KEY SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

Key secondary endpoints for this study are as follows:

1. Change in the TS-CGI score from baseline to week 12
2. Change in the TS-PGII score from baseline to week 12
3. Change in the C&A-GTS-QOL ADL subscale from baseline to week 12

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. Key Secondary Efficacy Analysis

8.3.1.1. Analysis of the change in the TS-CGI and C&A-GTS-QOL ADL subscale

The change in the TS-CGI score from baseline to week 12 (1st secondary endpoint) and C&A-GTS-QOL ADL subscale score from baseline to week 12 (3rd secondary endpoint) 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 TS-PGII

The change in the TS-PGII score from baseline to week 12 (2nd secondary endpoint) 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 12 is as follows:

[redacted]

8.3.2. Sensitivity Analysis

[redacted]

[redacted]

8.4. EXPLORATORY ENDPOINTS AND ANALYSIS

[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 ≤9 weeks, >9 to ≤12 and >12 weeks will also be summarized using descriptive statistics.

Also, the actual daily dose during each week in maintenance period will be summarized by treatment, age group, weight group, and CYP2D6 status. Furthermore, the frequency and percentage of patients reached the maximum daily dose allowed will be provided. Bar plot of patients reached the maximum daily dose will be presented. A Kaplan-Meier Curve will be used to present the time to the maximal dose in days by treatment, age group, weight group, and CYP2D6 status.

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 with requiring increased medication;
- Proportion of patients requiring decreased 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 (titration plus maintenance phase

plus follow-up period) and for the titration 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 12. If clinically significant laboratory abnormalities have been noticed at week 12 visit, those laboratory evaluations will be repeated at the week 13 visit. A list of laboratory tests is included in Table 4.

Observed values (in SI units) and change from baseline to week 12 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 12 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 phosphate sodium potassium chloride creatinine glucose magnesium blood urea nitrogen (BUN) total cholesterol uric acid alanine aminotransferase (ALT) aspartate aminotransferase (AST) lactate dehydrogenase (LDH) alkaline phosphatase (ALP) bicarbonate or carbon dioxide total protein albumin total bilirubin direct bilirubin	hemoglobin hematocrit red blood cell (RBC) count mean cell volume platelet count white blood cell (WBC) count, and differential count - absolute neutrophil count (ANC) - polymorphonuclear leukocytes (neutrophils) - lymphocytes - eosinophils - monocytes - basophils	protein glucose ketones blood (hemoglobin) pH specific gravity microscopic - bacteria - RBCs - WBCs - casts - crystals

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 12. 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 12. 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, 6, 9, 12, and 13. 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 12. BMI will be computed similarly as in Section 7.2 at week 12 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 end of treatment. 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, 6, and 12. 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 end of treatment 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 12. Physical examinations will not be summarized. Physical examinations will be listed.

9.11. NEUROLOGICAL EXAMINATIONS

Neurological examinations will be performed at screening and week 12. 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 andin the attempt to identify possible symptoms consistent with ADHD symptomatology, the items below from C&A-GTS-QOL were chosen:

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, 6, 9, 12, and 13. As the CDI-2 is designed for children 7 to 17 years of age, children 6 years of age at baseline will not complete the Self-report version; the caregiver/adult will complete the Parent version.

The CDI-2 self-report is a 28-item self-report questionnaire assessing depressive symptoms in children 7 to 17 years of age with basic reading and comprehension skills. In the CDI-2, children are asked to choose 1 of 3 statements that most closely aligns with their feelings in the previous 2 weeks. The 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, 6, 9, 12, and 13. 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. CHANGE 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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Su M, McFarlane F, Cavanna A, et al. The English Version of the Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL). J Child Neurol 2017;32(1):76-83.

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

14. PROGRAMMING CONSIDERATIONS

[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. INC Research SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

INC Research SOP 03.009 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

Summary number	Title	Population
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19. APPENDICES

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