Objectives	Endpoints
The **primary objective** of the study is to evaluate the efficacy of fixed doses of TEV-50717 to reduce motor and phonic tics associated with Tourette Syndrome (TS).	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.
Secondary objectives	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 the YGTSS from baseline to week 8 for low-dose TEV-50717 and placebo will be tested 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 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- scale (C&A-GTS-QOL) activities of daily living (ADL) subscale 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 The hierarchy of testing of secondary endpoints regarding dose level to control type I error is specified in the section entitled **"**Analysis of Key Secondary Endpoints."

Abbreviation	Term
CTA	Clinical Trial Application
CTFG	Clinical Trial Facilitation Group
[redacted]	[redacted]
CYP	cytochrome P4502D6
C&A-GTS-QOL	Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life scale
DMC	Data Monitoring Committee
DSM-V™	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	Ethics Committee
ECG	electrocardiogram
EMA	European Medicines Agency
ERA	European Regulatory Affairs
EU	European Union
EudraCT	European Clinical Trials
EV	EudraVigilance
GCP	Good Clinical Practice
GCO	Global Clinical Operations
GPSP	Global Patient Safety and Pharmacovigilance
GQA	Global Quality Assurance
GRA	Global Regulatory Affairs
[redacted]	[redacted]
HD	Huntington disease
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
INN	international nonproprietary name
IRB	Institutional Review Board
ITT	intent-to-treat
LAM	lactational amenorrhea methods

2.1.1. Justification of Primary Endpoint

[redacted]

2.2. Exploratory Endpoints

[redacted]

2.3. Safety Endpoints

Objectives	Endpoints
A **secondary objective** is to evaluate the safety and tolerability of TEV-50717.	The safety endpoints 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 and changes from baseline in electrocardiogram (ECG) parameters and shifts from baseline for clinically significant abnormal findings • observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis) In addition to routine monitoring of adverse events, clinical laboratory parameters, 12-lead ECGs and safety scales, an independent Data Monitoring Committee will monitor safety during the conduct of the study.

2.4. Pharmacokinetic Endpoint

The pharmacokinetics of the α-HTBZ and β-HTBZ metabolites of TEV-50717 will be explored based on sparse sampling (2 samples) at week 8.

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

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 the group to which they are randomized, body weight at baseline, and cytochrome P450 2D6 (CYP2D6) impairment status. 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, which will be used only by IRT for randomization into the study.

Prescreening period (up to 3 months before baseline): For patients who require discontinuation of certain prohibited concomitant medications 3 months before baseline (depot neuroleptics, botulinum toxin, or tetrabenazine), informed consent/assent, depending on the child's age, as appropriate, should be obtained prior to discontinuing the prohibited medication.

Screening period (up to 31 days): After informed consent/assent, depending on the child's age, as appropriate, is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation, including medical history, physical and neurological examination, laboratory testing, and 12-lead ECG, along with rating scales to assess severity, frequency, and impairment of tics and comorbid TS symptoms and behavioral status. The Mini International Neuropsychiatric Interview for Children and Adolescents, or MINI Kid, is a short questionnaire (largely yes/no questions) to screen for clinically significant underlying psychiatric illness that may affect the subject's eligibility. The assessment will focus on detecting major depression, mania/hypomania, obsessive/compulsive disorder, alcohol and substance abuse, attention deficit hyperactivity and conduct disorders, and psychotic disorders.

At the discretion of the investigator, the screening visit may be divided into 2 visits to reduce the burden on patients. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits. Patients will return to the clinic on day 1 for baseline procedures and to re-confirm eligibility. Patients may be rescreened 1 time if there is a change in the status of the patient regarding eligibility for the study. (Note: Details of rescreening must be approved and documented by the medical monitor and/or Clinical Surveillance and Training [CST] team.)

Treatment period (8 weeks): Patients who continue to remain eligible for participation in the study will be randomized at the baseline visit (day 1) and will receive blinded IMP to begin that same day (day 1). Tablets should be taken with food (eg, a snack) and should not be taken on an empty stomach. Patients and their caregiver/adult will interact regularly with the clinical research staff, either by telephone contact or clinic visit to assure adherence with study procedures and to evaluate safety and efficacy. To this end, clinic visits will be performed at weeks 2, 4, and 8 after baseline to evaluate safety; assess tic severity with the YGTSS, TS-CGI, TS-PGII, and the C&A-GTS-QOL; and perform safety rating scales to augment adverse event reporting, concomitant medication usage, clinical laboratory examination, and 12-lead ECGs. Telephone contacts will occur at the end of weeks 1, 3, 6, and 7.

As this is a fixed-dose study, patients will undergo dose escalation (ie, forced titration) to their target dose over the first 4 weeks of treatment. If a patient experiences depression, suicidal ideation or behavior, anxiety, akathisia, parkinsonism, or somnolence, or any other adverse event that interferes with daily activity, or any adverse event that is related to IMP, a single dose reduction is permitted. The investigator must discuss any further dose adjustments (eg, holding the dose or doses) with the medical monitor.

In case of such an adverse event, the investigator will determine if a dose reduction or suspension is necessary. If it is determined that a dose reduction or suspension is required, the medical monitor must be contacted. All available information, including the patient and caregiver/adult reports of adverse events, the clinical assessment of safety by the investigator, and information from rating scales should be incorporated in the decision. This reduced dose will become the patient's dose for the remainder of the study.

Patients will return to the clinic at week 8 for the final on-treatment assessment of safety and efficacy. At this visit, patients will undergo a complete evaluation, including performance of all efficacy measures (including assessment of tic severity with the YGTSS), and complete safety testing (including physical and neurological examination, safety laboratory testing, 12-lead ECG, and all rating scales). In addition, patients will undergo pharmacokinetic sampling at week 8, at which time 2 pharmacokinetic specimens will be obtained 2 to 3 hours apart. Prior to the clinic visit on week 8, patients will be reminded to record in their diary the start time of their last meal and the time of their last dose of study medication before the week 8 visit. The site will document the date and time of the sample collection.

Follow-up: All patients will discontinue IMP at the week 8 visit and will return 1 week later for evaluation of safety and tic reduction (week 9).

Patients who complete the study may be eligible to begin participation in an open-label safety extension Study 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 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).

The end of study is defined as the date of the week 10 telephone contact with the last participant.

Prohibited drugs will remain the same during the washout period for patients who will participate in the open-label extension Study TV50717-CNS-30047. Patients who will not participate in the extension study may begin/resume tic therapy medication after the first week of the washout period.

The study duration will be approximately 17 months from January 2018.

The study schematic diagram is presented in Figure 1.

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[a]			
	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

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

Pharmacokinetic data will be reviewed at the week 8 visit. Evaluation of pharmacokinetic data will include review of the measurement of plasma concentrations of TEV-50717 (deutetrabenazine), α-HTBZ, β-HTBZ, and other metabolites, as required.

3.5. Stopping Rules for the Study

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of the following:

- new toxicological or pharmacological findings or safety issues that invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the IMP

Table 2: Study Procedures and Assessments

	Prescreening	Screening	BL[a]	Escalation period (weeks)				Maintenance period (weeks)			Follow-up (weeks)		Unscheduled
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] (Day70)**	
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]			
Chemistry / hematology / urinalysis		X								X			X[j]

Table 2: Study Procedures and Assessments (Continued)

	Prescreening	Screening	BL[a]	Escalation period (weeks)				Maintenance period (weeks)			Follow-up (weeks)		Unscheduled
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] (Day70)**	
Visit window (days)			**0**	**±3 days**							**±3 days from week 8**		
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 Profiles)[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]		
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]

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

A reference sample is provided in Appendix O.

6.2.3. [redacted]

[redacted]

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

The C&A-GTS-QOL is administered at baseline, week 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).

A reference sample is provided in Appendix Q.

6.2.5. [redacted]

[redacted]

6.2.6. [redacted]

[redacted]

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse event, the study period is defined for each patient as the time period from signature of the informed consent/assent form to the end of the follow-up period. For this study, there will be 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 the open-label safety extension Study TV50717-CNS-30047.

For subjects who experience an adverse event or serious adverse event after signing a prescreening ICF for Study TV50717-CNS-30060, the event will be documented in the subject source documents and Electronic Data Capture (EDC) systems. For serious adverse events, the serious adverse event form must be completed in addition, and the serious adverse event must be reported immediately to the sponsor (Section 7.1.5.3.1). If the subject attends the screening visit, the adverse event or serious adverse event identified during the prescreening period will be considered medical history. For data entry purposes in EDC, the stop date for the prescreening adverse event or serious adverse event will be the date of the screening visit, and the start date for the associated medical history will be the date of the screening visit.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events, the serious adverse event form must be completed and the serious adverse event must be reported immediately (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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

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

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF.

The relationship of each adverse event to IMP and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Further details are given in the safety monitoring plan.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the following:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product

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

Table 5: The Relationship of an Adverse Event to the IMP

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

7.1.5. Serious Adverse Events

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

For recording of serious adverse event, the study period is defined for each patient as that time period from signature of the informed consent/assent form to the end of the follow-up period as defined in Section 7.1.2. Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death
- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

  Hospitalizations scheduled before the patient and caregiver/adult signed the informed consent/assent form will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as all of the below, must be reported by the investigator to the sponsor as a serious adverse event:

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

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

7.1.5.2. Expectedness

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

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

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the IMP, must be reported by the investigator according to the instructions provided on the serious adverse event form. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the LSO or designee (a CRO in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's GPSP.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility, reasonable possibility)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known

- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP, study procedures, and to underlying disease.

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

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/CRO for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Blinding will be maintained for all study personnel. Therefore, in case of a SUSAR, only the LSO/CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.2).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TEV-50717 and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study

7.2.1. Mini International Neuropsychiatric Interview for Children and Adolescents

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

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

A reference sample is provided in Appendix I.

7.2.2. Columbia-Suicide Severity Rating Scale

The C-SSRS children's baseline/screening scale assesses past and current suicidal ideation and behaviors to determine suicide risk and is administered at screening. C-SSRS children's SLV scale is administered at baseline and at weeks 2, 4, 8, and 9. Children 13 years of age and under may be interviewed separately or jointly with the caregiver/adult as appropriate or defined by the scale. For children over 13 years of age, caregiver/adult involvement is strongly encouraged. Questions should be directed to the child, but the caregiver/adult should be encouraged to add relevant information. The C-SSRS is an interview by trained study personnel.

Suicidal ideation

- Patients with a positive C-SSRS suicidal ideation score on either items 1 or 2 or a change on the CDI-2 Parent or Self-Report Profiles consistent with increasing depressive symptoms must be 1) discussed with the medical monitor, 2) re-evaluated within 2 to 3 days in a clinic visit, and 3) treated according to the investigator's medical judgment. Consultation with a child and adolescent psychiatrist or licensed child/adolescent mental health provider is advised, followed by close ongoing monitoring.
- If patients endorse or report a C-SSRS suicidal ideation level of 3, 4, or 5, subjects will be evaluated immediately by the study investigator and referred for psychiatric evaluation. The medical monitor will be immediately consulted. If it is determined by the investigator, after consultation with the medical monitor and the consulting psychiatrist, that exposure to the IMP may have contributed to this change in C-SSRS and/or increased depressive symptoms, IMP will be immediately discontinued and the patient terminated from the study. In cases where it is determined that IMP did not contribute to changes in depression or suicidality, the investigator will consult with

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 TS- PGII score from baseline to week 8 between high-dose TEV-50717-treated patients and placebo-treated patients
5. Change in the TS-PGII score from baseline to week 8 between low-dose TEV-50717-treated patients and placebo-treated patients
6. Change in the C&A-GTS-QOL ADL subscale 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

9.5.3. Exploratory Endpoints

9.5.4. Safety Endpoints

9.5.5. Planned Method of Analysis

The mITT analysis set (Section 9.2.2) will be used for all efficacy analyses. Summaries will be presented by treatment group.

9.5.5.1. Primary Efficacy Analysis

The primary efficacy endpoint for this study is the change in the TTS of the YGTSS from baseline to week 8 between high-dose TEV-50717-treated and placebo-treated patients. The primary analysis will be a mixed-model repeated-measures model 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 to 11 years, 12 to 16 years) will be included as covariates. The unstructured covariance matrix for repeated observations within patients will be used. The least squares means of the change in TTS from baseline at week 8 will be compared between the high-dose treatment arm and the placebo arm using a 2-sided test at the alpha = 0.05 level of significance. In addition, actual values and changes in the TTS from baseline to each visit will be summarized using descriptive statistics.

9.5.5.2. Sensitivity Analysis

Sensitivity analyses for missing data and the statistical model will be provided in the statisitical analysis plan.

9.5.5.3. Key Secondary Efficacy Analyses

A hierarchical (fixed-sequence) testing approach will be used for the analysis of the key secondary endpoints. If an endpoint is not statistically significant, confirmatory hypothesis testing will not be not carried out on the remaining hypotheses, and remaining hypotheses will be considered exploratory rather than confirmatory. The following analyses of key secondary endpoints will be conducted:

1. The change from baseline to week 8 in TS-CGI will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent variable and baseline YGTSS TTS as a covariate, the corresponding TS-CGI values will be used. The comparison between high-dose TEV-50717 and placebo will be tested.
2. Using the same model as for the primary analysis, the comparison between the change in the TTS of the YGTSS from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.
3. Using the same model as described in endpoint #1 above for TS-CGI, the comparison between the change in the TS-CGI values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.
4. The change from baseline to week 8 in TS-PGII will be analyzed using a Cochran-Mantel-Haenszel-row mean score test with modified ridit scoring controlling for age group. The comparison between high-dose TEV-50717 and placebo will be tested.
5. Using the same model as described in endpoint #4 above for TS-PGII, the comparison between the change in the TS-PGII values from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.
6. The change from baseline to week 8 in the C&A-GTS-QOL ADL subscale will be analyzed using a similar model as the primary analysis; however, instead of change in YGTSS TTS as the dependent variable and baseline YGTSS TTS as a covariate, the

- obtain a blood sample (3 mL) for analysis of CYP2D6 genotype
- perform a serum pregnancy (beta-human chorionic gonadotropin [β-HCG]) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For Mini International Neuropsychiatric Interview for Children and Adolescents [MINI Kid] and Columbia Suicide Severity Rating Scale [C-SSRS], 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 YGTSS questionnaire should be performed before any blood draws or ECG assessments.):
  - MINI Kid (Note: The following modules will be used: Major Depressive Episode [Module A], [Hypo] Manic Episode [Module D], obsessive-compulsive disorder [OCD; Module J], Alcohol Dependence/Abuse [Module L], Substance Dependence/Abuse [Non-alcohol; Module M], Attention Deficit Hyperactivity Disorder [ADHD; Module O], Conduct Disorder [Module P], and Psychotic Disorders and Mood Disorders with Psychotic Features [Module R])
  - Children's Depression Inventory Second Edition (CDI-2), Parent and Self-report Profiles (Note: Children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.)
  - C-SSRS (children's baseline/screening)
  - YGTSS (Input from the caregiver/adult is required.)
- assess of adverse events
- review medication history and concomitant medications

3. **Procedures Before Administration of Investigational Medicinal Product (Baseline, Day 1)**

Patients who meet the inclusion and exclusion criteria at screening will continue to the day 1 visit, when baseline assessments will be conducted. The YGTSS, Tourette Syndrome-Clinical Global Impression (TS-CGI), Tourette Syndrome-Patient Global Impression of Impact (TS-PGII), and [redacted] questionnaires should be performed before any blood draws or ECG assessments.

The following procedures will be performed at the day 1 visit/baseline:

- randomization
- conduct clinic visit
- review eligibility (inclusion and exclusion) criteria
- measure vital signs (orthostatic pulse and BP [after standing for at least 3 minutes], body temperature, and respiratory rate) and weight (Note: Weight must be measured with shoes and outerwear off.)

Exploratory Endpoints:

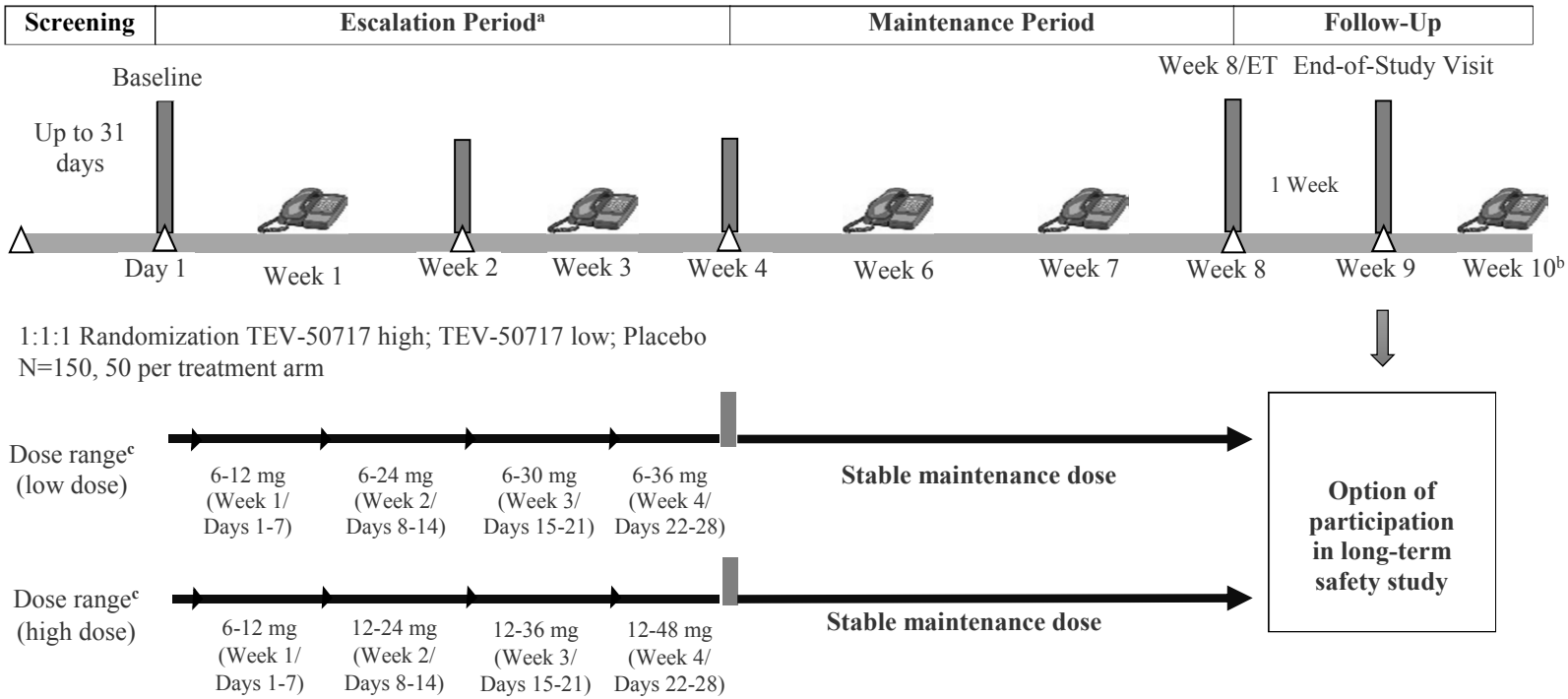
[redacted]

Safety Endpoints:

Objectives	Endpoints
A **secondary objective** is to evaluate the safety and tolerability of TEV-50717.	The safety endpoints 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 and changes from baseline in electrocardiogram (ECG) parameters and shifts from baseline for clinically significant abnormal findings • observed values and changes from screening in clinical laboratory parameters (hematology, chemistry, and urinalysis) In addition to routine monitoring of adverse events, clinical laboratory

Abbreviation	Term
LSO	local safety officer
MAA	Marketing Authorisation Application
MINI Kid	Mini International Neuropsychiatric Interview for Children and Adolescents
mITT	modified intent to treat
MTD	maximum tolerated dose
[redacted]	[redacted]
n	number
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	Non-Investigational Medicinal Products
NOAEL	no-observed-adverse-effect level
OCD	obsessive-compulsive disorder
OTC	over-the-counter
PD	pharmacodynamics
PGx	pharmacogenetics
PND	postnatal day
PP	per-protocol
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	Regulatory Affairs
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
SpO_2	saturation of peripheral oxygen
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	elimination half-life
TD	tardive dyskinesia
TS	Tourette syndrome
TS-CGI	Tourette Syndrome-Clinical Global Impression
TS-PGII	Tourette Syndrome-Patient Global Impression of Impact
[redacted]	[redacted]
TTS	Total Tic Score

Figure 1: Overall Study Schematic Diagram



[a] If a stable dose is reached before the indicated time, the patient should continue taking that dose for the remainder of the escalation period and throughout the maintenance period. See Table 1 for the maximum dose of IMP and escalation by CYP impairment status, week, and baseline body weight category.

[b] This is a telephone contact for safety evaluation, required only for patients who will not participate in the open-label safety extension study for TEV-50717.

[c] Ranges account for different dosing schedules for patients with baseline weight ≥40 kg; ≥40 kg, CYP impaired; 30 to <40 kg; 30 to <40 kg, CYP impaired; 20 to <30 kg; and 20 to <30 kg, CYP impaired. See Table 1 for daily dose by category.

CYP=cytochrome P4502D6; CYP impaired=patients who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer; ET=early termination visit.

Note: An unscheduled visit will require a clinic visit.

3.6. Schedule of Study Procedures and Assessments

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. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 2: Study Procedures and Assessments (Continued)

	Prescreening	Screening	BL[a]	Escalation period (weeks)				Maintenance period (weeks)			Follow-up (weeks)		Unscheduled
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] (Day70)**	
Visit window (days)			**0**	**±3 days**							**±3 days from week 8**		
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. If the screening visit is divided into 2 visits, the blood sample should be obtained during the first of the 2 visits.
[f] Patients will be provided with a diary at baseline, week 2, week 4, and at unscheduled visits, 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 caregiver/adult. 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 (ie, from week 1 to week 4).
[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.

6.2.7. [redacted]

- modifying the existing consent/assent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TEV-50717

7.1.6. Protocol-Defined Adverse Events of Special Interest

No protocol-defined adverse events of special interest were identified for this study.

7.1.7. Withdrawal Due to an Adverse Event

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

In addition, a blood sample should be obtained for the measurement of IMP concentrations, if possible. The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made). The investigator must inform the clinical project physician/clinical leader as soon as possible of any patients who are being considered for withdrawal due to adverse event(s). Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that, in the opinion of the investigator, is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

7.1.8. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Psychometric Rating Scales

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

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

Suicidal behavior

- Actual attempt:
  - If patients report any suicidal behavior that is an actual attempt as assessed in the C-SSRS, they will be evaluated immediately by the study investigator, referred for psychiatric evaluation, and terminated from the study.
- Interrupted attempt, aborted attempt, or Preparatory Acts or Behavior:
  - If patients report any suicidal behavior that is interrupted, aborted, or preparatory as assessed in the C-SSRS, they will be evaluated immediately by the study investigator and referred for psychiatric evaluation. In cases where it is determined in the psychiatric evaluation that IMP did not contribute to changes in suicidal behavior, the investigator will consult with the medical monitor, the consulting psychiatrist, and/or sponsor to determine whether the patient should continue in the study.

A reference sample is provided in Appendix K.

7.2.3. Children's Depression Inventory, Second Edition

The CDI-2 (Parent and Self-report Profiles) is administered at screening; baseline; and weeks 2, 4, 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 questionnaire covers both the major and minor symptoms of depression as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (Sun and Wang 2015).

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

A reference sample is provided in Appendix J.

7.3. Pregnancy

Any female patient becoming pregnant during the study will discontinue IMP.

All pregnancies of female patients participating in the study that occur during the study, or within 14 days after the end of the study, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The

corresponding C&A-GTS-QOL ADL subscale values will be used. The comparison between high-dose TEV-50717 and placebo will be tested.

7. Using the same model as described in endpoint #6 above for the C&A-GTS-QOL ADL subscale, the comparison between the change in the C&A-GTS-QOL ADL subscale scores from baseline to week 8 for low-dose TEV-50717 and placebo will be tested.

9.5.5.4. Exploratory Analyses

[redacted]

- perform 12-lead ECG (Note: ECG will be performed after at least 5 minutes rest in a supine or semi-supine position.)
- perform serum pregnancy (β-HCG) test (only in females who are postmenarchal or ≥12 years of age)
- administer the following questionnaires (Note: For C-SSRS, [redacted] and Child and Adolescent Gilles de la Tourette Syndrome - Quality of Life scale (C&A-GTS-QOL), 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 YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.):
  - CDI-2, Parent and Self-report Profiles (Note: Children 6 years of age at baseline will not complete the self-report version; the caregiver/adult will complete the parent version.)
  - C-SSRS (children's Since Last Visit [SLV])
  - YGTSS (Input from the caregiver/adult is required.)
  - TS-CGI
  - TS-PGII (Input from the caregiver/adult is permitted.)
  - [redacted]
  - [redacted]
  - [redacted]
  - C&A-GTS-QOL
- dispense investigational medicinal product (IMP) (patients will receive doses for 2 weeks [current dose level and next dose level] to cover the telephone contacts)
- provide patients with a diary to record critical information on dosing
- assess of adverse events
- review concomitant medications

4. **Procedures During Administration of Investigational Medicinal Product**

   a. **Escalation Period (Weeks 1 and 3) and Maintenance Period (Week 6)**

Patients who meet the inclusion and exclusion criteria at screening will continue to visit 1, when baseline assessments will be conducted. The YGTSS, TS-CGI, TS-PGII, and [redacted] questionnaires should be performed before any blood draws or ECG assessments.