

2. SYNOPSIS

Name of Sponsor/Company: Teva Global Branded Products R&D, Inc.	Individual study table referring to part of dossier in which the individual study or study table is presented	(For National Authority Use Only)
Name of Finished Product: TEV-50717		
Name of Active Ingredient: Deutetrabenazine		
	Volume:	
	Reference:	

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

Investigators and Study Centers: The study was conducted at 36 centers in the United States, Canada, Denmark, Russian Federation, Serbia, and Spain. A complete list of investigators and their affiliations is included in the clinical study report.

Publication (reference): None

Study Period: 05 February 2018 to 12 November 2019 **Phase of Development:** 2/3

Primary Objective: The primary objective of the study was to evaluate the efficacy of TEV-50717 to reduce motor and phonic tics associated with TS.

Secondary Objectives: The secondary objective of the study was to evaluate the safety and tolerability of titration and maintenance therapy with TEV-50717.

Number of Patients (Planned and Analyzed): For this study, 116 patients were planned to be enrolled; data from 117 patients were analyzed for efficacy and data from 117 patients were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Patients were included in the study if all of the following main criteria were met (not all inclusive):

- Patient was 6 to 16 years of age, inclusive, at baseline.
- Patient weighed at least 44 pounds (20 kg) at baseline.
- Patient met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V™) diagnostic criteria for Tourette syndrome (TS) and, in the opinion of the investigator, patient, and caregiver/adult, the patient's active tics were causing distress or impairment.
- Patient had a Total Tic Score (TTS) of 20 or higher on the Yale Global Tic Severity Scale (YGTSS) at screening and baseline.
- Patient and caregiver/adult were willing to adhere to the medication regimen and to comply with all study procedures.
- Patient was in good general health, as indicated by medical and psychiatric history as well as physical and neurological examination.

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Main Criteria for Exclusion: Patients were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- Patient had a neurologic disorder other than TS that could obscure the evaluation of tics.
- Patient had a confirmed diagnosis of bipolar disorder, schizophrenia, or another psychotic disorder.
- Patient had clinically significant depression at screening or baseline.
- Patient had a history of suicidal intent or related behaviors within 2 years of screening
 - previous intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence, at the time of suicidal thought
 - previous suicidal preparatory acts or behavior
- Patient had a first-degree relative who had completed suicide.
- Patient had clinically significant obsessive-compulsive disorder (OCD) at baseline that, in the opinion of the investigator, was the primary cause of impairment.
- Patient had received Comprehensive Behavioral Intervention for Tics for TS or cognitive behavioral therapy for OCD within 4 weeks of screening.
- Patient had received any of the following concomitant medications within the specified exclusionary windows of screening, baseline, or first dose: depot neuroleptics, botulinum toxin, or tetrabenazine (3 months of first dose); cannabidiol oil and valbenazine (4 weeks); reserpine (21 days); and neuroleptics (oral), typical and atypical antipsychotics, metoclopramide, levodopa, and dopamine agonists; (14 days).
- Patient had a QT interval corrected for heart rate using Fridericia’s formula (QTcF) interval value >450 msec (males) or >460 msec (females) or >480 msec (with right bundle branch block) on 12-lead ECG at screening OR required treatment with drugs known to prolong the QT interval.
- Patient had evidence of hepatic impairment, renal impairment, unstable or serious medical illness at screening or baseline.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:

Investigational Product: TEV-50717 oral tablets at strengths of 6, 9, 12, 15, and 18 mg were used. Study drug was dispensed in the clinic. Patients received doses for 2 weeks at the baseline, week 2, and week 4 visits (current dose level and next dose level) to cover the telephone contacts. At the week 6 and week 9 visits, patients received doses for 3 weeks.

TEV-50717 was administered as oral tablets at a starting dose of 6 mg. Titration schemes based on body weight at baseline are shown in the table below. The maximum daily dose was determined by body weight and CYP2D6 impairment status at baseline. Although dose adjustments could be made up to and including the week 7 telephone call, if a stable dose was reached before then, the patient was to continue taking that dose for the remainder of the titration period and throughout maintenance dosing. If a patient experienced a “clinically significant” adverse event that was attributed to study drug, the investigator was to determine if a dose reduction or suspension was necessary. At the end of the titration period, the patient’s dose was established for the maintenance period. If a patient experienced an adverse event during the maintenance period and the investigator believed a dose reduction was warranted, the dose could be reduced.

Study day ^a	Weight category					
	20 to <30 kg		30 to <40 kg		≥40 kg	
CYP impairment status	Not impaired	Impaired	Not impaired	Impaired	Not impaired	Impaired
Days 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
Days 8-14	12 mg	12 mg	12 mg	12 mg	18 mg	18 mg
Days 15-21	18 mg	18 mg	18 mg	18 mg	24 mg	24 mg
Days 22-28	18 mg	18 mg	24 mg	24 mg	30 mg	30 mg
Days 29-35	24 mg	18 mg	30 mg	24 mg	36 mg	36 mg
Days 36-42	24 mg	18 mg	36 mg	24 mg	42 mg	36 mg
Days 43-49	30 mg	18 mg	42 mg	24 mg	48 mg	36 mg

^a Administration of a given dose took place throughout the days indicated. The new dose started 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 received 6 mg on days 1 and 2 and 12 mg starting on day 3.

CYP=cytochrome P450; CYP2D6=cytochrome P450 2D6

Note: CYP-impaired patients are those patients who were receiving a strong CYP2D6 inhibitor or who were a CYP2D6 poor metabolizer. The investigator, in consultation with the patient and caregiver/adult, determine if a dose increase was warranted to achieve optimal tic reduction.

Placebo: The placebo tablets and packaging matched those for TEV-50717.

Information regarding the batches of study drug that were used in this study is available upon request.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: Patients were randomly assigned to receive TEV-50717 or matching placebo (1:1) stratified by age at baseline (6 to 11 years and 12 to 16 years). Patients were centrally randomly assigned to the treatment groups by means of a computer-generated randomization list after confirmation of all eligibility criteria. The randomization list and treatment were assigned to the relevant treatment groups through a qualified service provider (ie, via Interactive Response Technology [IRT]).

Duration of Treatment: Treatment continued for 12 weeks; up to 7 weeks of titration, followed by 5 weeks of maintenance.

General Design and Methodology: This was a Phase 2/3, randomized, double-blind, placebo-controlled, parallel-group study in which patients with tics associated with TS were invited to participate. Patients who qualified for the study were centrally randomized in a 1:1 ratio (stratified by age at baseline [6 to 11 years and 12 to 16 years]) to receive either TEV-50717 or matching placebo.

Throughout the study, patients interacted 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 was based on body weight and CYP2D6 impairment status at baseline. Patients were classified as CYP2D6 impaired if they were receiving a strong CYP2D6 inhibitor at baseline or were a CYP2D6 poor metabolizer based on a blinded assessment of CYP2D6 genotype. CYP2D6 impairment status was used by IRT for randomization into the study. The dose of study drug for each patient was titrated to an optimal level followed by maintenance therapy at that dose. Investigators were blinded to the cytochrome P450 (CYP) status, with a dose cap for poor metabolizers prespecified by the IRT.

Prescreening period: For patients who required discontinuation of certain prohibited concomitant medications within specified periods before screening, baseline, or the first dose of study drug (eg, use of depot neuroleptics,

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botulinum toxin, or tetrabenazine was prohibited within 3 months of baseline), informed consent/assent, depending on the child's age, as appropriate, was 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, was obtained, patients who were stable from a medical and psychiatric standpoint underwent a screening evaluation, including medical history, physical and neurological examination, laboratory testing, and 12-lead electrocardiogram (ECG), along with rating scales to assess severity, frequency, and impairment of tics and comorbid TS symptoms and behavioral status. At the discretion of the investigator, the screening visit may have been divided into 2 visits to reduce the burden on patients.

Treatment period: The overall treatment period was 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. Site administered scales, conducted electronically, include the YGTSS, [REDACTED], and the Columbia-Suicide Severity Rating Scale (C-SSRS). Self-administered scales include the Tourette Syndrome-Patient Global Impression of Impact (TS-PGII); [REDACTED]; [REDACTED] Children's Depression Inventory, Second Edition (CDI-2); and Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life (C&A-GTS-QOL). For the YGTSS, input from the caregiver/adult was required. For both the TS-PGII and [REDACTED], input from the caregiver/adult was permitted. For all other scales, for children 13 years of age and under, interviews were 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 was strongly encouraged. Questions were to be directed to the child, but the caregiver/adult was encouraged to add relevant information. It should be noted that the CDI-2 has individual parent and child questionnaires.

Follow-up: All patients were to discontinue study drug at the week 12 visit and return 1 week later for evaluation of safety and tic reduction (week 13). Patients who completed the study were 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 could choose to enter Study TV50717-CNS-30047 (on that day) or had an additional week to make a decision and return for day 1. Patients not participating in Study TV50717-CNS-30047 had a follow-up telephone contact to evaluate safety 1 week after the end of the washout period (2 weeks after their last dose of study drug).

The end of study is defined as the date of the week 14 visit of the last patient.

Primary Efficacy Measure(s) and Endpoint(s): The primary efficacy endpoint is the change in YGTSS-TTS from baseline to week 12.

Secondary Efficacy Measures and Endpoints: The secondary efficacy variables and endpoints are as follows:

- change in the TS-Clinical Global Impression (TS-CGI) score from baseline to week 12
- change in the TS-PGII score from baseline to week 12
- change in the C&A-GTS-QOL activities of daily living (ADL) subscale score from baseline to week 12

Safety Variables: The safety endpoints for this study were as follows:

- incidence of adverse events
- observed values and changes from baseline in vital signs
- observed values and change from baseline in the CDI-2 and Parent and Self-Report Profiles
- observed values in the C-SSRS

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- observed values in 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)

Pharmacokinetics: Blood samples were obtained for the measurement of plasma concentrations of TEV-50717 (deutetrabenazine), α -HTBZ (dihydrotrabenazine), β -HTBZ, and the total ($\alpha + \beta$) HTBZ. Blood sampling for pharmacokinetic (PK) analysis was performed at the week 12 visit. Two samples were collected. The first sample was collected upon arrival at the clinic. The second sample was collected 2 to 3 hours after the first PK sample collection.

Statistical Considerations: The statistical methods applied and the sample size calculations were as stated in the protocol and described in the sections below. Details of the methodology are expanded in the statistical analysis plan, which was approved before the treatment codes were revealed.

All data were processed and summarized by the use of SAS[®] Version 9.3. Unless otherwise specified, all statistical tests are 2-sided using a 0.05 level of significance. All confidence intervals (CIs) are 2-sided 95% CIs.

Analysis Populations

The intent-to-treat (ITT) analysis set included all randomized patients. In this population, treatment was assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. The ITT analysis set was used for all study population summaries, unless otherwise noted. Summaries were presented by treatment group and for all patients. Patient listings on efficacy data were based on the ITT analysis set.

The modified intent-to-treat (mITT) analysis set included all patients in the ITT population who received at least 1 dose of study drug and had both a baseline and at least 1 post-baseline YGTSS assessment. In this population, treatments were assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. All efficacy analyses were based on the mITT analysis set.

The safety analysis set included all patients who received at least 1 dose of study drug. In this population, treatments were assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized. All safety analyses and listings were based on the safety analysis set.

Efficacy Analyses

The primary efficacy analysis was a mixed-model, repeated-measures (MMRM) with the change in TTS as the dependent variable. The model included 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 to 11 years and 12 to 16 years) were included as covariates. The unstructured covariance matrix for repeated observations within patients was used.

The least squares (LS) mean of the change in TTS from baseline at week 12 was compared (the TEV-50717 arm and the placebo arm) using a 2-sided test at the $\alpha=0.05$ level of significance.

In order to assess the robustness of the primary efficacy analysis, sensitivity and supplementary analyses were performed. These included analyses for missing data, the statistical model, and analysis using the ITT analysis set.

The LS mean and standard error (SE) for the treatment groups and the LS mean difference, 95% CI, and p-value for the comparison (TEV-50717 versus placebo at week 12) were presented.

A hierarchical (fixed-sequence) testing approach was 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 was not statistically significant,

confirmatory hypothesis testing was not carried out on the remaining hypotheses, and remaining hypotheses were considered exploratory rather than confirmatory.

Summary of Results

Patient Disposition and Demography:

Disposition: A total of 140 patients with TS were screened for enrollment into this study. Of the 140 patients screened, 119 patients met the entry criteria and were considered to be eligible for randomization in the study. Of the 119 patients randomized, 117 received at least 1 dose of study drug and were evaluated for efficacy and safety in the study; 2 patients withdrew before taking any study drug.

A total of 12 (10%) patients withdrew from the study (8 [14%] receiving TEV-50717 and 4 [7%] receiving placebo treatment). The highest overall rate of withdrawal was observed in the TEV-50717 group. The most frequent reason for withdrawal was withdrawal by patient, which occurred for 5 patients in the TEV-50717 group and 2 patients in the placebo group.

Demographics and Baseline Characteristics: The TEV-50717 and placebo groups were well matched with regard to age (mean 11.5 years, for each group), gender (89.8% and 85.0% male, respectively), and race (83.1% and 88.3% white, respectively).

Baseline characteristics were generally similar between patients in each treatment group in the ITT analysis set. Mean times since TS diagnosis for the TEV-50717 and placebo groups were 3.05 and 2.95 years, respectively. Mean baseline YGTSS-TTS for patients in the 2 groups were 31.7 and 33.0, respectively. Greater than 81% of patients were CYP2D6 not impaired. Mean BMIs were 21.2 and 21.8 kg/m² for the TEV-50717 and placebo groups, respectively. Among all patients, 63.0% were ≥ 40 kg, and 13.0% and 31.0% were categorized in the BMI categories of overweight and obese, respectively.

Medical history was comparable between the treatment groups, with the exception of the proportion of patients with psychiatric disorders (TEV-50717, 81.4%; placebo, 66.7%) and with ADHD (TEV-50717, 62.7%; placebo, 51.7%).

The TEV-50717 and placebo groups were comparable in their use of any prior medications and therapies (TEV-50717, 28.8%; placebo, 30.0%). In general, the medications taken were consistent with the patients' known medical histories. The groups were comparable in their prior use of antidepressant medications (3 [2.5%] patients; TEV-50717, 2 [3.4%]; placebo, 1 [1.7%]). The use of ADHD medication was higher in the TEV-50717 group compared with the placebo group (14 [11.8%] patients; TEV-50717, 10 [16.9%]; placebo, 4 [6.7%]). The TEV-50717 and placebo groups were comparable in their prior Tourette syndrome treatment, with 31 (52.5%) patients and 26 (43.3%) patients, respectively.

Efficacy Results: The primary efficacy endpoint, the change in the YGTSS-TTS from baseline to the end of therapy at week 12, did not show a statistically significant difference between the TEV-50717 and placebo groups. The reduction from baseline in LS mean (SE) was 9.1 (1.28) in the TEV-50717 group and 8.4 (1.25) in the placebo group, for a treatment effect of -0.7 ($p=0.692$, $d=-0.073$).

Sensitivity and supplementary analyses performed for missing data, for the statistical model, and for the ITT analysis set supported the robustness of the efficacy findings in the primary analyses, ie, the difference between the TEV 50717 and placebo groups in the change from baseline to week 12 in the YGTSS-TSS was not statistically significant

Analyses of the YGTSS-TTS change from baseline over time showed that the differences (LS mean difference) between the TEV-50717 and placebo groups increased from baseline to week 9 and was clinically meaningful at weeks 6 (LS mean= -3.3, nominal $p=0.031$) and 9 (LS mean= -3.6, nominal $p=0.033$).

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Because of the hierarchical testing approach taken and the lack of statistical significance of the primary endpoint, all of the key secondary endpoints are considered exploratory.

The first key secondary efficacy endpoint was the change in the TS-CGI score from baseline to week 12. The reduction from baseline in LS mean (SE) was 0.7 (0.13) in the TEV-50717 group and 0.7 (0.12) in the placebo group, for a treatment effect of 0.0 (nominal $p=0.849$). The mean reductions from baseline to the weeks prior to week 12 in the TS-CGI score showed a trend in favor of the TEV-50717 group.

The second key efficacy endpoint was the change in the TS-PGII score from baseline to week 12. The reduction in the mean (SE) TS-PGII score from baseline to week 12 was 0.7 (0.18) in the TEV-50717 group and 0.4 (0.14) in the placebo group (nominal $p=0.053$). The mean reductions from baseline to the all weeks, including week 12, in the TS-PGII score showed a trend in favor of the TEV-50717 group.

The third key efficacy endpoint was the change in the C&A-GTS-QOL ADL subscale score from baseline to week 12. The reduction from baseline to week 12 in LS mean (SE) was 9.9 (2.37) in the TEV-50717 group and 8.8 (2.27) in the placebo group, for a treatment effect of -1.1 (nominal $p=0.731$). The mean reductions from baseline to the assessment prior to week 12 in the C&A-GTS-QOL ADL subscale score showed a trend in favor of the TEV-50717 group.

In the weeks prior to week 12, the secondary endpoints showed a similar trend to the primary endpoint. The mean reductions from baseline to the weeks prior to week 12 in scores of the TS-CGI and C&A-GTS-QOL ADL subscale showed trends that favored the TEV-50717 group compared with the placebo group. For TS PGII, improvements favoring the TEV-50717 group when compared to the placebo group were seen at all weeks, including week 12.

Safety Results: During the overall period (titration, maintenance, and follow-up periods), 38 (65.5%) patients in the TEV-50717 group and 33 (55.9%) patients in the placebo group reported at least 1 adverse event. The most common adverse event (>4% of patients in either of the treatment groups) overall during the study was headache in 12 (10.3%) of all patients. Other frequently occurring adverse events (those occurring in 4 or more patients in the TEV-50717 group than in the placebo group) were weight increased (7 [12.1%] vs. 1 [1.7%]), fatigue (7 [12.1%] vs. 3 [5.1%]), somnolence (5 [8.6%] vs. 1 [1.7%]), and enuresis (4 [6.9%] vs. 0 [0%]). Upper respiratory tract infection occurred in 7 (11.9%) patients in the placebo group and no patients in the TEV-50717 group.

Most adverse events for patients in both the TEV-50717 and placebo groups were reported as mild or moderate in severity. Only 5 patients (4 in the TEV-50717 group and 1 in the placebo group) had severe adverse events. Treatment-related adverse events (reasonable possibility of relationship) in the overall period were reported for 29 (50.0%) patients in the TEV-50717 group and 12 (20.3%) patients in the placebo group.

There were no deaths during the study. There were no other SAEs during the overall period; one patient had an SAE during the screening period and was not randomized into the study. Two patients, 1 (1.7%) each in the TEV-50717 group and the placebo group, withdrew from treatment due to treatment-emergent adverse events.

A total of 9 (7.7%) patients, 4 (6.9%) in the TEV-50717 group and 5 (8.5%) in the placebo group, had an adverse event(s) leading to dose interruption. Each adverse event leading to dose interruption was reported in 1 patient in either the TEV-50717 group or the placebo group.

A total of 8 (6.8%) patients, 7 (12.1%) patients in the TEV-50717 group and 1 (1.7%) patient in the placebo group, had an adverse event(s) leading to dose reduction. The most frequent reason for dose reduction was fatigue in 2 patients in the TEV-50717 group and 1 patient in the placebo group. All other events leading to dose reduction were reported in 1 patient each and in 1 treatment group each.

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Weight increased was experienced by 7 (12%) patients in the TEV-50717 group and 1 (2%) patient in the placebo group. A slight difference in TEV-50717 and placebo groups mean BMI percentage change from baseline to week 12 (3.91% vs 0.29%) was also observed.

To increase the sensitivity of detecting class-related adverse events, the frequencies of key adverse events by SMQ preferred terms of suicide/self-injury, depression (excluding suicide and self-injury), and Parkinson-like events were determined in a supportive analysis in the safety analysis set. These events occurred at low frequency in the TEV-50717 and placebo groups.

One (1.7%) patient in the TEV-50717 group and 3 (5.1%) patients in the placebo group had adverse events within the suicide/self-injury SMQ. The patient in the TEV-50717 group had a history of suicidal ideation and was taking the antidepressant fluoxetine for obsessive compulsive disorder. The onset of the adverse event of suicidal ideation occurred during the titration phase; the event had a duration of 1 day (resolved on the same day) and was considered mild in severity, with a reasonable possibility of being related to study drug. The dose was not changed and the patient recovered. The 3 adverse events of suicidal ideation in the patients in the placebo group were considered mild in severity, with the dose of study drug interrupted for 1 patient and not changed for the other 2 patients. Two of the 3 adverse events were considered to have a reasonable possibility of being related to study drug. The 3 patients recovered from the events.

One of the patients in the placebo group with suicidal ideation also had an adverse event of intentional self-injury. The suicidal ideation occurred at the end of the maintenance period (study day 83); the intentional self-injury occurred during the follow-up period (study day 88). The intentional self-injury was considered mild in severity with no reasonable possibility of relationship to study drug. The dose was not changed, and the patient recovered from both adverse events.

Six patients in the TEV-50717 group and 3 patients in the placebo group had adverse events within the depression (excluding suicide/self-injury) SMQ.

Safety scales assessed during the study indicated that there was no signal detected for increased symptoms of ADHD, depression, or suicidality. There were no differences between the TEV-50717 and placebo groups in laboratory (serum chemistry, hematology, urinalysis), vital sign, ECG, or physical examination findings during the study.

Pharmacokinetics Results: These data will be available in a separate PK report.

Conclusions:

- TEV-50717 was not effective in reducing tics (YGTSS-TTS) from baseline to week 12 of treatment (primary endpoint) as compared with placebo. A trend towards a greater reduction of tics (YGTSS-TTS) from baseline was observed at assessments prior to week 12. A similar trend was observed that favored the TEV-50717 group for the secondary endpoints of TS-CGI and C&A-GTS-QOL ADL at assessments prior to week 12. For TS PGII, improvements favoring the TEV-50717 group when compared to the placebo group were seen at all weeks, including week 12.
- Overall, TEV-50717 was generally well tolerated. No deaths or serious adverse events occurred in this study. Only 5 patients (4 in the TEV-50717 group and 1 in the placebo group) had severe adverse events, and 1 patient in each group withdrew from study drug due to adverse events. There were no trends in changes from baseline in serum chemistry, hematology, urinalysis, vital sign, ECG, physical and neurological parameters. There was no evidence of a new safety signal in pediatric patients with TS treated with TEV-50717 in comparison to the known safety profile of this drug in adult patients with HD or TD.