NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA efficacy supplement
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Priority or Standard	Priority
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Division/Office	DP/ON/OND
Review Completion Date	06/28/2021
Established/Proper Name	Deutetrabenazine
(Proposed) Trade Name	Austedo
Pharmacologic Class	Vesicular monoamine transporter 2 (VMAT2) inhibitor
Code name	TEV-50717
Applicant	Teva Branded Pharmaceutical Products R&D, Inc.
Dosage form	Tablet
Applicant proposed Dosing Regimen	N/A
Applicant Proposed Indication(s)/Population(s)	Updates to section 8.4 of labeling (neg. studies)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	N/A
Recommendation on Regulatory Action	N/A (Pediatric supplement for negative study; labeling added)
Recommended Indication(s)/Population(s) (if applicable)	N/A
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N/A
Recommended Dosing Regimen	N/A

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
ADL=Associate Director of Labeling (DP)

Glossary

ADHD	attention deficit hyperactivity disorder
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BDI	Beck Depression Inventory
BMI	body mass index
BPM	beats per minute
C&A-GTS-QOL	Gilles de la Tourette Syndrome–Quality of Life Scale for Children and Adolescents
CBIT	Comprehensive Behavioral Intervention for Tics
CBT	cognitive behavioral therapy
CDI-2	Children's Depression Inventory Second Edition
CFB	change from baseline
CFR	Code of Federal Regulations
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
HD	Huntington's disease
ICH	International Council for Harmonisation
IND	Investigational New Drug
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NMS	neuroleptic malignant syndrome
OCD	Obsessive Compulsive Disorder
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PK	pharmacokinetics
PRO	patient reported outcome
PWR	Pediatric Written Request
SAE	serious adverse event
SOC	System Organ Class
SMQ	standardized MedDRA query
TEAE	treatment emergent adverse event
TD	tardive dyskinesia
TS	Tourette Syndrome
TS-CGI	Tourette Syndrome-Clinical Global Impression
TS-PGII	Tourette Syndrome-Patient Global Impression of Impact
TTS	total tic score

YBOCS	Yale-Brown Obsessive Compulsive Scale
YGTSS	Yale Global Tic Severity Scale

1 Executive Summary

1.1. Product Introduction

Deutetrabenazine (TEV-50717) is a deuterium-substituted form of tetrabenazine, which acts as a vesicular monoamine transporter 2 inhibitor (VMAT2 inhibitor). Tetrabenazine is approved for the treatment of chorea associated with Huntington's disease (HD). The deuterium substitution was designed to slow elimination, reduce variability in plasma levels, and decrease dosing frequency. Deutetrabenazine is approved for the treatment of chorea associated with HD and for the treatment of tardive dyskinesia (TD) in adults. In this efficacy supplement, the Applicant has submitted the results of clinical studies that evaluated the effect of deutetrabenazine in pediatric Tourette Syndrome (TS). These studies were intended to fulfill a Pediatric Written Request (PWR) and the Applicant has submitted a request for pediatric exclusivity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant completed a 12-week flexible-dose study and an 8-week, fixed-dose study in pediatric patients with (TS); both were adequate and well-controlled. Deutetrabenazine did not demonstrate either a statistically significant or clinically meaningful treatment effect on tics associated with pediatric TS.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tourette Syndrome (TS) is a chronic and frequently impairing neurodevelopmental disorder. Current pharmacologic treatment options are limited and additional treatments are needed. Adequate and well-controlled studies of deutetrabenazine in pediatric patients with TS failed to demonstrate a clinically meaningful treatment effect. Pediatric safety information from the studies submitted with this application will be included in labeling (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• TS is a neurodevelopmental disorder characterized by motor and vocal tics. TS typically presents in early childhood and can impede activities of daily living, impair functioning, and impact the psychological well-being of individuals with TS and their caregivers.	• TS can negatively impact multiple health outcomes during critical phases of development and is a pediatric public health concern.
Current Treatment Options	• Three antipsychotic medications are currently approved for the treatment of TS: haloperidol, aripiprazole, and pimozide. Serious risks associated with use of these medications include extrapyramidal symptoms, neuroleptic malignant syndrome (NMS), QTc prolongation, and sedation. Weight gain and adverse metabolic effects may occur with aripiprazole.	• Pediatric patients with TS would benefit from additional pharmacologic treatment options.
Benefit	• The efficacy of deutetrabenazine was evaluated in two randomized, double-blind, placebo-controlled studies in pediatric patients ages 6 to 16 years with TS. The primary efficacy endpoint in both studies was the change in the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) from baseline to the end of therapy. • In Study 30046, a 12-week flexible-dose study, the placebo-subtracted least squares means difference in YGTSS-TTS from baseline to end of treatment was -0.7 (95% CI: -4.1, 2.8).	• No statistically significant or clinically meaningful treatment effect of deutetrabenazine was found in the completed clinical studies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In Study 30060, an 8-week fixed dose study, the placebo-subtracted least squares means difference in YGTSS-TTS from baseline to end of treatment was -0.8 (95% CI: -3.9, 2.3) for the high-dose group. The effect in the low-dose group was not formally tested.	
Risk and Risk Management	• The most commonly reported adverse events in patients receiving deutetrabenazine were headache, somnolence, fatigue, increased appetite, and increased weight.	• Adequate and well-controlled studies of deutetrabenazine failed to demonstrate a treatment effect in pediatric patients with TS. Deutetrabenazine carries risks of potentially impairing adverse reactions. Therefore, the benefit:risk profile of deutetrabenazine in pediatric patients with TS is unfavorable. Section 8.4 of the Prescribing Information will be updated with pediatric safety information obtained from the submitted studies (b) (4) [redacted]

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

x	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	8.1.2, 8.2.4, 8.2.6
		x	Observer reported outcome (ObsRO)	8.1.2, 8.2.4, 8.2.6
		x	Clinician reported outcome (ClinRO)	8.1.2, 8.2.4
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by the presence of multiple motor tics and one or more vocal tics. The Diagnostic and Statistical Manual of Mental Disorders (DSM 5) criteria specify that tics must have persisted for at least 1 year since first tic onset and that onset occurs prior to 18 years of age (American Psychiatric Association 2013). The motor and vocal tics need not occur concurrently. The typical age of onset is between 5 and 8 years and the average age of diagnosis is 8 years (Bitsko et al. 2014). Tic severity usually intensifies in mid-childhood and declines during adolescence and adulthood. Prevalence of TS in children and adolescents is estimated to be 0.5% to 1%. TS frequently co-occurs with psychiatric conditions including attention deficit-hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), depression, and anxiety. TS has been associated with impaired social functioning, difficulties completing activities of daily living, physical pain, suicidal ideation, and significant caregiver burden (Robertson et al. 2017).

2.2. Analysis of Current Treatment Options

Comprehensive Behavioral Intervention for Tics (CBIT), a manualized habit-reversal and relaxation training program, is the recommended first-line treatment for pediatric patients with tics associated with TS (Pringsheim et al. 2019).

Three medications are currently approved for the treatment of TS. Haloperidol is indicated for the treatment of tics and vocal utterances associated with TS in children and adults, though approved labeling notes that safety and efficacy in pediatric patients have not been established. Aripiprazole has been evaluated in and is approved for use in children and adolescents ages 6 to 18 years with TS. Pimozide is indicated for the suppression of vocal and motor tics associated with TS that fail to respond to standard treatments. Limited data on the safety and efficacy of pimozide in children less than 12 years of age are available. All FDA-approved medications for TS are dopamine antagonists and carry risks of neuroleptic malignant syndrome (NMS) and tardive dyskinesia. Haloperidol and pimozide prolong the QT interval. Sudden death, which may be related to QT interval prolongation, has occurred following pimozide treatment. The approved medications are also associated with sedation/drowsiness. Weight gain and adverse metabolic effects may occur with aripiprazole.

Off-label pharmacologic treatments for TS include other atypical or typical antipsychotics, alpha agonists, and topiramate. Botulinum toxin injections have been used in adolescents and adults with localized symptoms. Deep brain stimulation is typically reserved for severe, self-injurious tics (Pringsheim et al. 2019).

Table 1: Summary of Treatment Armamentarium Relevant to Pediatric TS

Product (s) Name	Relevant Indication	Dosing/ Administration	Important Safety and Tolerability Issues
Haloperidol	Control of tics and vocal utterances of Tourette's disorder in children and adults	Children: 0.05 mg/kg/day to 0.075 mg/kg/day orally Adults: no Tourette-specific dose recommendations. General dose range – 0.5 mg BID to 5 mg TID orally	Cardiovascular effects including QTc prolongation; neuroleptic malignant syndrome; tardive dyskinesia; increased mortality in elderly patients with dementia-related psychosis; hematologic effects
Aripiprazole	Treatment of Tourette's disorder	Patients < 50 kg: 2 mg/day to 10 mg/day orally Patients ≥ 50 mg: 2 mg/day to 20 mg/day orally	Cerebrovascular adverse reactions in elderly patients with dementia-related psychosis; neuroleptic malignant syndrome, tardive dyskinesia; metabolic changes; pathological gambling and other compulsive behaviors; orthostatic hypotension; hematologic effects; seizures/convulsions; cognitive and motor impairment; suicide
Pimozide	Use in patients with Tourette's disorder whose symptoms are severe and who cannot tolerate, or who do not respond to, haloperidol	Children 12 years and older: 0.05 mg/kg/day to 0.2 mg/kg/day orally (maximum 10 mg/day) Adults: 1 mg/day to 10 mg/day orally	QTc prolongation, neuroleptic malignant syndrome, tardive dyskinesia; hematologic effects; ventricular arrhythmias with macrolide antibiotics; sudden death

Source: U.S. Prescribing Information for haloperidol, aripiprazole, and pimozide

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Deutetrabenazine was approved for the treatment of chorea associated with Huntington's disease (HD) in April 2017 (NDA 208082) and for the treatment of tardive dyskinesia (TD) in adults in August 2017 (NDA 209885). The August 2017 approval letter administratively closed NDA 209885 and directed submissions for this product (trade name Austedo) to NDA 208082.

(b) (4)

(b) (4)

Orphan drug designation was granted for treatment of TS in the pediatric population (0 to 16 years of age) in June 2015.

3.2. Summary of Presubmission/Submission Regulatory Activity

A Type B preIND meeting was held on January 21, 2016. At this meeting, the Division and Applicant reached general agreement on the primary efficacy endpoint, the change from baseline on the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS). The Division also advised that at least one of the efficacy and safety studies (b) (4) should have a fixed-dose design.

The IND was submitted in March 2016 and placed on clinical hold because of inadequate juvenile animal data. After subsequent communications with the Applicant (including a Type A teleconference), the clinical hold was removed in August 2017.

The Applicant and the Division discussed the TS clinical development program during a Type B End of Phase 2 (EOP2) teleconference on August 22, 2017. The Division provided feedback on various elements of the study designs, including the testing hierarchy, plan for ECG monitoring, dosing, restriction of QT prolonging medications, and statistical methods.

The Applicant submitted a Proposed Pediatric Study Request in October 2019. The Agency issued a Pediatric Written Request (PWR) in January 2020.

The PWR requires two adequate and well-controlled pharmacokinetic, efficacy, and safety studies in patients 6 to 16 years with TS. One study must be a fixed-dose study that evaluates multiple doses, with doses based on weight and CYP2S6 impairment status. The PWR specifies that the two-arm study must have at least 116 patients, that the three-arm study must have at

least 150 patients, and that the primary efficacy endpoint must be the YGTSS-TTS. The WR also requires a long-term safety study in this patient population.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were requested for this application.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

SD-809 (deutetrabenazine) is a deuterated form of tetrabenazine. Two hydrogen atoms on tetrabenazine have been replaced with deuterium atoms in order to slow down the rate of metabolism of the two primary active metabolites of tetrabenazine, α- and β-dihydrotetrabenazine. Deuterium substitution of tetrabenazine does not produce any novel metabolites, but it does produce quantitative differences in metabolites. The pharmacologically active major metabolites of tetrabenazine, α- and β-dihydrotetrabenazine, and the deuterated versions formed from metabolism of deutetrabenazine, d6-α-dihydrotetrabenazine and d6-β-dihydrotetrabenazine, are antagonists of the vesicular monoamine transporter 2 (VMAT2), a protein involved in the transport of neurotransmitters into synaptic vesicles.

The definitive juvenile toxicity study conducted in rats treated orally with SD-809 at doses of 2.5, 5, and 10 mg/kg/day revealed that juvenile rats are more sensitive than adult rats to the adverse CNS effects of SD-809. There was also a significant decrease in body weight and food consumption for males at 5 and 10 mg/kg/day throughout the entire dosing period and for females only during the first few weeks. CNS-related adverse clinical signs including tremors, hypoactivity, splayed hindlimbs, hunched posture, and closed eyelids were observed immediately after dosing in males and females at the mid and high doses. Hyperactivity was observed prior to dosing in almost all animals at 10 mg/kg/day and several at 5 mg/kg/day, which continued into the first week of the recovery phase at 10 mg/kg/day. Juvenile animals also exhibited an increase in arousal/activity, motor activity, and startle response. There was a slight delay in attainment of vaginal patency in high dose females (indicative of a slight delay in sexual maturation), but the effect was attributed to lower body weights. The NOAEL was determined to be 2.5 mg/kg/day due to adverse CNS signs at 5 and 10 mg/kg/day. The NOAEL in previously conducted adult rat studies was 5 mg/kg/day. Young juvenile rats (postnatal day 20) had much greater exposure to parent (SD-809; 10-fold higher) than older juvenile and adult rats. This effect was greater in male rats compared to females. Metabolite levels (α+β-HTBZ) in male juvenile rats were similar across age ranges; however, in female juvenile rats, levels of α+β-HTBZ were higher in younger rats compared to adult rats. The age-related differences in parent and metabolite plasma exposure could be due to age-related differences in metabolizing enzymes in rats (e.g., CYP2D6). The age-related differences in exposure ratios of parent drug (SD-809) to active metabolites may also explain the increased sensitity of juvenile rats to the CNS effects of the drug compared to adult rats.

Nonclinical studies submitted to support this supplemental NDA included three juvenile rat toxicity studies:

- Study No. SD-809-NC-055: A Twice Daily Oral (Gavage) Toxicity and Toxicokinetic Study of Deuterated Tetrabenazine (SD-809) in Juvenile Rats

- Study No. DS-2017-035: d6 β-Dihydrotetrabenazine (SD-949) and SD-809: 46-Day Toxicity Study via Twice Daily (BID) Oral Gavage in Juvenile Rats with Reproductive Evaluation during the Recovery Period

- Study No. DS-2016-061: SD-1021: 9-Week Toxicity Study via Twice Daily Oral Gavage in Juvenile Rats with Reproductive Evaluation During the Recovery Period

d6 β-Dihydrotetrabenazine (SD-949) is a major, active metabolite of deutetrabenzaine (SD-809) and SD-1021 is a minor metabolite of deutetrabenazine. No adverse toxicities were observed in rat juvenile toxicity studies conducted with d6 β-Dihydrotetrabenazine (SD-949) or SD-1021 (reviews included in Appendix, Section 19.3.)

5.2. Referenced NDAs, BLAs, DMFs

(b) (4)

IND 120631 and NDA 209885: submitted by the Applicant and approved for tardive dyskinesia.

5.3. Pharmacology

Deutetrabenazine (SD-809) is a selective deuterium-substituted form of tetrabenazine. Tetrabenazine undergoes extensive first pass metabolism to produce the major active metabolites, alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ); both are potent inhibitors of vesicular monoamine transporter-2 (VMAT2). The major metabolites of deutetrabenazine, deuterated (d)6-α-HTBZ and d6-β-HTBZ also inhibit VMAT2 (IC_{50s} of 0.0082 and 0.047 µM, respectively). Off-target binding of deutrabenazine was similar to what has been reported for tetrabenazine.

5.4. Toxicology

No new genetic toxicology studies submitted.

5.4.1. Reproductive and Developmental Toxicology

Study title: A twice daily oral (gavage) toxicity and toxicokinetic study of deuterated tetrabenazine (SD-809) in juvenile rats

Study no.:	SD-809-NC-055
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 8, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SD-809, lot no. DT21213001, 99.83%

Key Study Findings

- Decrease in body weight and food consumption for males at ≥ 5 mg/kg/day throughout the entire dosing period and for females during the first few weeks.
- CNS-related adverse clinical signs after dosing for males and females at ≥ 5 mg/kg/day. Increased startle response for males at ≥ 5 mg/kg/day
- Effects on various FOB observations indicating increased arousal/activity for males at ≥ 5 mg/kg/day and females at 10 mg/kg/day. All reversible. Increased motor activity at ≥ 5 mg/day (partially reversible).
- Age-related differences in parent and metabolite plasma exposure, PND 21 rats up to 10-fold higher exposure to parent (SD-809) than metabolites compared to levels on PND 31 and 70.
- NOAEL = 2.5 mg/kg/day due to adverse CNS signs at 5 and 10 mg/kg/day. Exposure to total (α+β)-HTBZ (SD-948 + SD-949) at 2.5 mg/kg/day on PND 21 compared to highest pediatric values in humans (1301 ng.hr/ml) is 0.22 for both males and females.

Methods

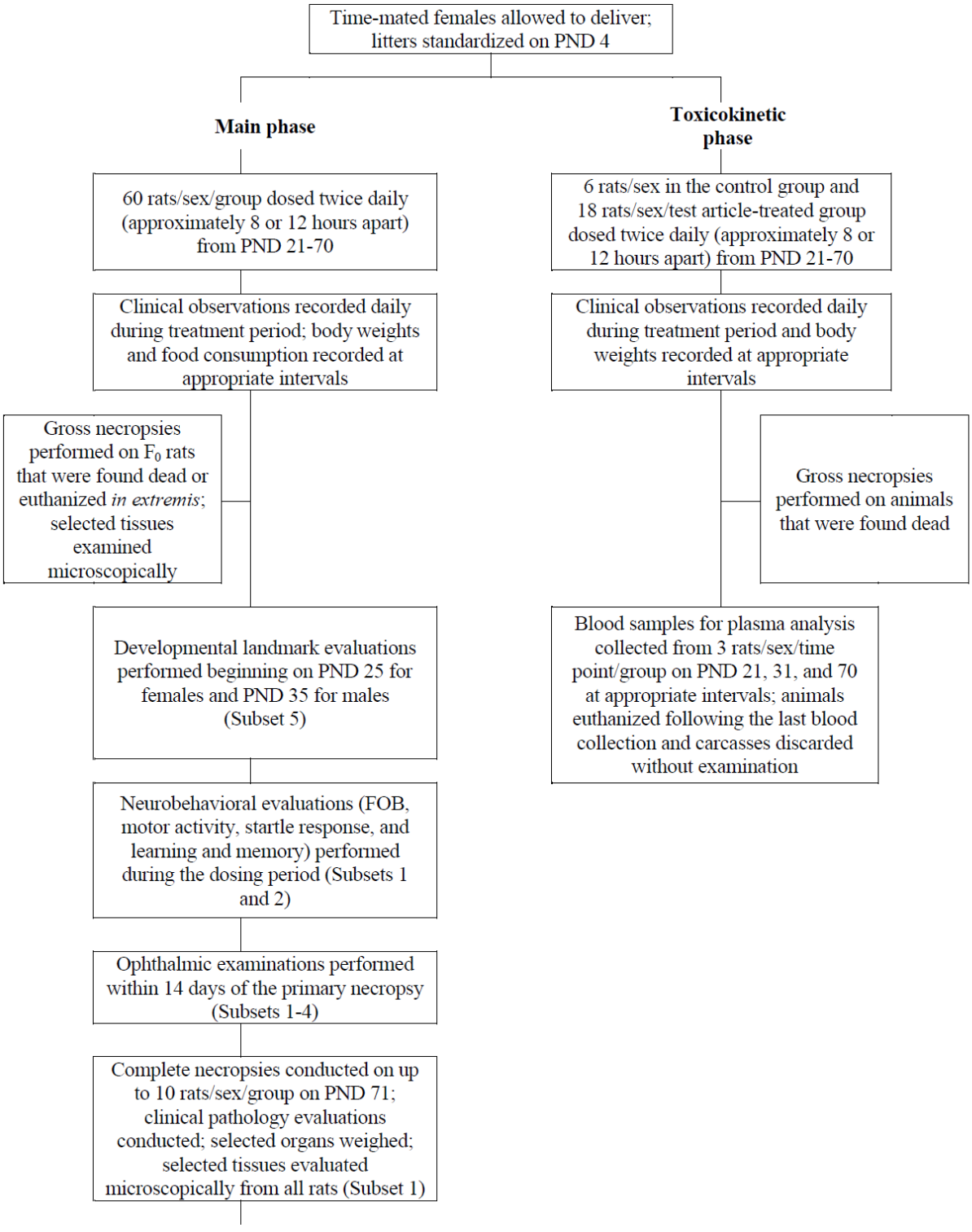
Doses:	0, 2.5, 5, 10 mg/kg/day (0, 1.25, 2.5, 5 mg/kg BID)
Frequency of dosing:	Twice daily (approximately 8-12 hrs apart)
Route of administration:	Oral gavage
Dose volume:	2.38, 2.27, 2.27, 2.38 ml/kg/dose, respectively
Formulation/Vehicle:	0.5% carboxymethyl cellulose (medium viscosity) with 0.1% (w/v) polysorbate 80 in deionized water/suspension
Species/Strain:	Rat/Sprague-Dawley (Crl:CD(SD)) Time-mated females were received from (b) (4) and allowed to deliver. Litters culled on postnatal day (PND) 4. Weaned juveniles were housed together by litter until PND 28. Beginning on PND 28, 2-3 juveniles were housed per cage by sex.
Number/Sex/Group:	60/sex/group
Age:	21 days at dosing initiation
Weight:	At dosing initiation: Males: 34-68 g, females: 29-62 g.
Satellite groups:	Toxicokinetic satellite groups: 6/sex/control; 18/sex/drug-treated groups
Deviation from study protocol:	None that affected study or data integrity.
Dosing formulation analysis:	All dosing formulations were within 88.0% to 97.7% of target concentrations, except the first preparation of the group 2 (0.5 mg/ml) which was 79.9% of target. All subsequent preparations for group 2 were >88% of target.

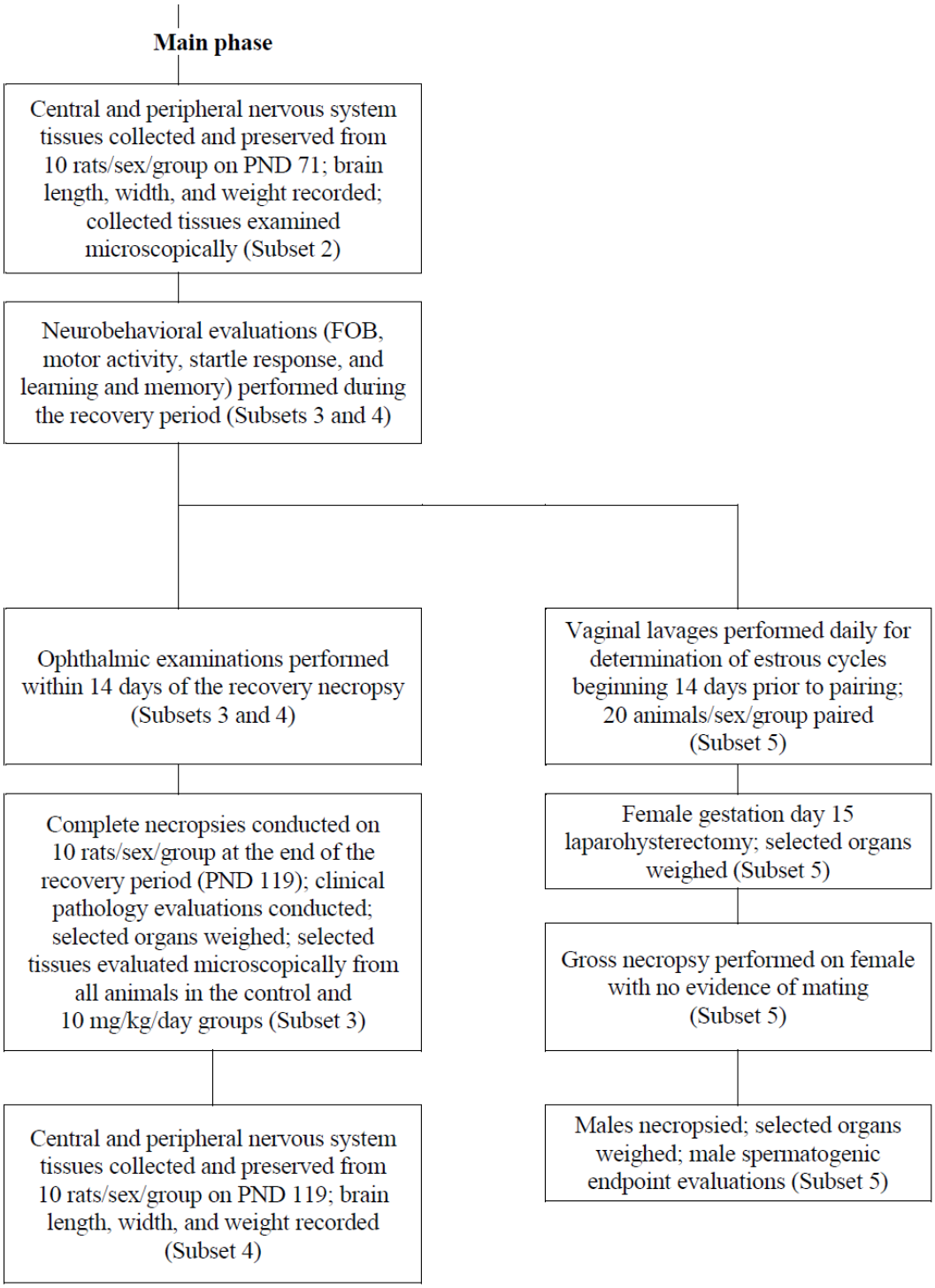
Dose Selection

Dose selection was based on study SD-809-NC-054: A 21-day twice daily oral (gavage) toxicity and toxicokinetic study of deuterated tetrabenazine (SD-809) in juvenile rats.

Study Design

Figure 1: SD-809-NC-055 Study Design





[Diagram source: study no. SD-809-NC-055]

Observations and Results

Mortality

There were no deaths attributed to the drug. One male and one female each at 5 mg/kg/day were euthanized *in extremis* due to mechanical injuries. Two males at 10 mg/kg/day were found dead; one on PND 28 and the other on PND 48. Microscopic examination revealed that

the male that died on PND 48 died from an acute pulmonary hemorrhage; and therefore, the death was not considered drug-related. No cause of death was determined for the other male, but there was no significant effect on body weight and clinical signs observed in that male were similar to surviving animals in the same dose group.

Clinical Signs

There was a drug-related increase in CNS-related clinical signs observed throughout the entire dosing phase for the majority of males and females at 5 and 10 mg/kg/day approximately 1 hour after the first and second daily doses. The CNS-related clinical signs included increased incidences of tremors, hypoactivity, splayed hindlimbs, hunched posture, and partial closure of the eyes. At the daily examinations, an increased incidence of hyperactivity was observed for the majority of males and females at 10 mg/kg/day throughout the entire dosing phase and continued into the first week of the recovery phase. Hyperactivity was also observed during daily examinations in 8 and 13 males and females, respectively at 5 mg/kg/day during. The tremors and hyperactivity correlated with increased motor activity and FOB findings in the 5 and 10 mg/kg/day group males and females and were considered to be adverse. There were no drug-related findings at 2.5 mg/kg/day. Clinical signs were recorded daily (prior to dose administration) throughout the study beginning on the first day of dosing. Main phase pups were also observed ~1 hr following each daily dose administration.

Body Weights

Mean body weight and body weight gain was statistically significantly decreased for males at 5 and 10 mg/kg/day compared to controls, and the effect was adverse at 10 mg/kg/day. During the recovery period, body weight gain was generally similar to controls for males at 5 and 10 mg/kg/day, however, mean absolute body weight values were still statistically significantly decreased at the end of the recovery period 5.8% and 13.8% compared to controls, respectively. For females, there were instances of statistically significant decreases in mean body weight and body weight gain at 5 and 10 mg/kg/day compared to controls during the first few weeks of dosing. However, the effect was transient as there was no statistically significant effect on mean body weight at the end of the dosing period or an effect on overall body weight gain compared to controls. Mean body weight and body weight gain for females at 5 and 10 mg/kg/day was similar to controls during the recovery period. The effects on body weight for males and females correlated with decreases in food consumption. There was a significant decrease in body weight gain at 2.5 mg/kg/day for both males and females for the first couple of days following dosing administration, however the effect was transient and there were no overall effects on body weight or body weight gain at 2.5 mg/kg/day. There was no drug-related effect on body weight for females during the gestation period. Body weights were recorded daily from PND 21-28 and then twice weekly until the day of euthanasia. Body weights were also recorded for subset 5 females after evidence of mating on gestation days (GD) 0, 3, 6, 9, 12, and 15.

Table 2: Body Weight Gain (BWG) during the dosing phase (PND 20-70)

	Males	Females

Dose (mg/kg/day)	BWG (g) (% control)	BWG (g)
0	370	203
2.5	361 (-2.4%)	208
5	344** (-7.0%)	206
10	313** (-15%)	202

** significantly different from concurrent control p<0.01

Food Consumption

There was a statistically significant decrease in food consumption throughout most of the dosing phase for males and females at ≥ 5 mg/kg/day compared to controls, which correlated with decreases in body weight. Food consumption was similar to controls during the recovery period, with the exception of a slight, significant, decrease observed for males and females at 10 mg/kg/day during the first few days of the recovery period from PND 71-73. There was no effect on food consumption at 2.5 mg/kg/day for either males or females. There was no drug-related effect on food consumption for females during the gestation period. Individual food consumption was measured twice weekly from PND 28 until day of euthanasia.

Ophthalmoscopy

There were no drug-related findings.

Hematology

There were no adverse drug-related effects on any parameter; any finding was reversible and within historical control values. At the primary necropsy, there was a statistically significant decrease in absolute lymphocyte counts for males at 10 mg/kg/day compared to controls, with a slight, non-significant decrease at 5 mg/kg/day. The values were still within the historical control range for the laboratory and the effect was not present at the end of the recovery period, therefore the finding was not considered toxicologically relevant. Also, at the primary necropsy, females at 10 mg/kg/day had higher fibrinogen levels compared to controls, but this value was also within the historical control range and not present at the end of the recovery period, therefore the finding was not considered toxicologically relevant.

Clinical Chemistry

There were a few instances of statistically significant, drug-related, effects at the primary necropsy including higher blood urea nitrogen and lower serum calcium levels for 10 mg/kg/day males and increased aspartate aminotransferase for males and females at 10 mg/kg/day. However, these changes were not considered toxicologically relevant since the values were within the historical control range for the laboratory and similar findings were not observed in recovery group animals.

Urinalysis

There were no drug-related findings.

Gross Pathology/Organ weights

There were no drug-related macroscopic findings or effects on organ weights.

Histopathology

Adequate Battery: Yes, including neuropathology assessment
Peer Review: No
Histological Findings:
A decrease in cellularity of follicles and/or germinal centers was observed in the axillary lymph nodes and/or spleen of 2 males at 5 mg/kg/day and 4 males at 10 mg/kg/day; however, the finding was attributed to a decrease in body weight and/or age of animals and none correlated with clinical chemistry parameters. The findings were not seen in recovery animals indicating complete recovery.

Table 3: Histopathologic findings, PND 71

	Males				Females			
Dosage (mg/kg/day):	**0**	**2.5**	**5**	**10**	**0**	**2.5**	**5**	**10**
Lymph node, axillary [a]	**10**	**10**	**10**	**9**	**10**	**0**	**0**	**10**
Reduced cellularity, Follicles	0	0	1	3	0	-	-	0
Minimal	-	-	1	-	-	-	-	-
Mild	-	-	-	2	-	-	-	-
Moderate	-	-	-	1	-	-	-	-
Reduced Cellularity, Germinal Centers	0	0	2	3	0	-	-	0
Minimal	-	-	-	1	-	-	-	-
Mild	-	-	1	-	-	-	-	-
Moderate	-	-	1	1	-	-	-	-
Severe	-	-	-	1	-	-	-	-
Spleen [a]	**10**	**10**	**10**	**9**	**10**	**0**	**0**	**10**
Reduced Cellularity, Follicles	0	0	1	1	0	-	-	0
Minimal	-	-	1	-	-	-	-	-
Mild	-	-	-	1	-	-	-	-
Reduced Cellularity, Germinal Centers	0	0	1	3	0	-	-	0
Mild	-	-	-	1	-	-	-	-
Moderate	-	-	1	1	-	-	-	-
Severe	-	-	-	1	-	-	-	-

[a] - Number of tissues examined from each group.

[Table source: study no. SD-809-NC-055]

Table 4: Individual severity of histopathologic findings in axillary lymph nodes and spleen, PND 71

Animal ID	Axillary Lymph node		Spleen		Lymph[a]
	Reduced cellularity, Follicles	**Reduced cellularity, Germinal Centers**	**Reduced cellularity, Follicles**	**Reduced cellularity, Germinal Centers**	
Dosage: 5 mg/kg/day					
33496-02	Minimal	Moderate	Minimal	Moderate	14.23
33552-03	---	Mild	---	---	9.55
Dosage: 10 mg/kg/day					
33565-01	Mild	Moderate	---	---	8.15
33538-04	Moderate	Severe	Mild	Severe	14.88
33559-03	Mild	Minimal	---	---	9.43
33539-02	---	---	---	Mild	13.02

[a] Absolute lymphocyte count, thousand/uL

[Table source: study no. SD-809-NC-055]

Neuropathology evaluation:

No drug-related findings were observed. 10 animals/sex/group were macroscopically examined for neuropathology on PND 71 (subset 2) or at the end of the recovery period on PND 119 (subset 4). Animals were perfused *in situ* with fixative (4% paraformaldehyde). 11 brain slices were examined, along with spinal cord (cervical and lumbar), cervical and lumbar dorsal and

ventral root fibers and ganglia, sciatic nerves, sural nerves, tibial nerves, peroneal nerves, optic nerves, eyes, and skeletal muscle.

Special Evaluation

Developmental landmarks:
There was no statistically significant effect on the time to reach balanopreputial separation in males. The mean ages of attainment of balanopreputial separation were 44.8, 45.6, and 45.3 days in the 2.5, 5, and 10 mg/kg/day groups, respectively, compared to 43.5 days in the control group. In contrast, there was a drug-related effect in the time to reach vaginal patency for females, which was dose-related and statistically significant at 10 mg/kg/day compared to controls. The mean ages of attainment of vaginal patency were 33.5, 34.7, and 35.6 days in the 2.5, 5, and 10 mg/kg/day groups, respectively, compared to 32.8 days in the control group. Although the value for high dose females was within the (b) (4) historical control range (31.3 to 37.0 days), this delay was still considered to be drug-related and could not be attributed to a decrease in body weight.

Table 5: Developmental landmarks in males and females

MALES

GROUP:	0 MG/KG/DAY	2.5 MG/KG/DAY	5 MG/KG/DAY	10 MG/KG/DAY
BALANOPREPUTIAL SEPARATION (PND)				
MEAN	43.5	44.8	45.6	45.3
S.D.	2.15	2.41	2.46	3.28
S.E.	0.62	0.69	0.74	0.95
N	12	12	11	12
BODY WEIGHT (GRAMS)				
MEAN	227.6	234.6	227.3	206.5**
% DIFFERENCE		3.1	-0.1	-9.3
S.D.	18.62	12.29	16.62	12.26
S.E.	5.37	3.55	5.01	3.54
N	12	12	11	12

PND= POSTNATAL DAY
** = Significantly different from the control group at 0.01

FEMALES

GROUP:	0 MG/KG/DAY	2.5 MG/KG/DAY	5 MG/KG/DAY	10 MG/KG/DAY
VAGINAL PATENCY (PND)				
MEAN	32.8	33.5	34.7	35.6**
S.D.	2.04	1.68	1.87	2.84
S.E.	0.59	0.48	0.54	0.82
N	12	12	12	12
BODY WEIGHT (GRAMS)				
MEAN	110.2	113.5	113.7	114.8
% DIFFERENCE		3.0	3.2	4.2
S.D.	9.12	10.26	13.52	15.28
S.E.	2.63	2.96	3.90	4.41
N	12	12	12	12

PND= POSTNATAL DAY
** = Significantly different from the control group at 0.01

[Tables source: study no. SD-809-NC-055]

FOB Assessments:
There were several instances of drug-related and statistically significant findings in various FOB parameters related to increased arousal in the animals, however all findings were completely reversible when assessed at the end of the recovery period.

Home cage observations:
On PND 61, there was an increase in the number of animals that exhibited rearing for males at ≥ 5 mg/kg/day and for females at 10 mg/kg/day compared to controls. The values were

statistically significant for males, but not females. During the recovery period on PND 108, the incidence of rearing in drug-treated groups was similar to the control groups indicating complete reversibility. There was also a significant increase in the number of male pups at 10 mg/kg/day exhibiting eyelids wide open and alert and consequently a decrease in the number of pups with eyelids completely shut and asleep. This finding was also completely reversible in the recovery groups.

Handling observations:
There was a statistically significant increase in the number of pups that were described with a "slight resistance to being handled" and consequently a significant decrease in the number of pups that were "very easy" to remove from the cage or had "no resistance" to being handled for both males and females at 10 mg/kg/day. The incidence rates for these observations were similar to controls for drug-treated groups during the recovery period on PND 108.

Open field observations:
There was a statistically significant increase in the number pups that had increased arousal and described as "somewhat high arousal: slight excitement, tense, sudden darting or freezing" for males and females at 10 mg/kg/day on PND 61. The incidence rates were similar to controls during the recovery phase on PND 108. There was also a significant increase in the number of rearing counts for males at 10 mg/kg/day (55% increase compared to controls) and for females at ≥ 5 mg/kg/day (38% increase compared to controls) on PND 61. During the recovery period on PND 108, rearing counts in drug-treated groups were similar to controls.

Sensory:
There was a significant increase in the number of male pups at 10 mg/kg/day that had a more energetic startle response and a more energetic tail pinch response compared to controls on PND 61. Although females at 10 mg/kg/day did not reach statistically significant differences in these responses, there was also a trend for more energetic startle and tail pinch responses. Startle and tail pinch responses were comparable to controls for high dose males during the recovery period on PND 108.

Neuromuscular:
There were no statistically significant differences in any neuromuscular observations.

Physiological:
There was a statistically significant increase in body temperature for males at 5 and 10 mg/kg/day, 38.2°C, 38.3°C, respectively compared to 37.6°C for controls and for females at 10 mg/kg/day, 38.3°C compared to 37.8°C for controls. Body temperatures were comparable to controls during the recovery period on PND 108.

Motor Activity:
There was a marked, statistically significant, dose-related, increase in motor activity counts for males and females at ≥ 5 mg/kg/day (total cumulative activity counts increased 120% and 376% for males and 57% and 100% for females compared to controls, at 5 and 10 mg/kg/day,

respectively). Increases were observed at all time-points (from 0-60 min. post-dose) both in total and ambulatory motor activity counts. On PND 108, near the end of the recovery period, there was still a trend for an increase in both total and ambulatory counts for mid and high dose males and for high dose females, but the effect was much less than on PND 61.The increase in motor activity is most likely due to the pharmacology of the tetrabenazine being a vesicular monoamine transporter type 2 (VMAT2) inhibitor.

Auditory Startle response:
There was a statistically significant, dose-related increase in peak startle response for mid and high dose males on PND 62, but not on PND 108 indicating a complete recovery.

Learning and Memory Assessment:
There were no drug-related effects on learning and memory endpoints, as assessed using a water-filled 8-unit T-maze (Biel maze).

Reproductive performance:
There were no drug-related effects on any male or female mating, fertility or reproductive parameters, spermatogenesis endpoints, macroscopic findings or effects on organ weights in any animals assigned to the breeding phase.

Gestation day 15 laparohysterectomy:
There were no drug-related effects on any intrauterine parameters from animals that were assigned to the breeding phase, including pre-implantation loss, post-implantation loss, or the mean numbers of viable embryos, corpora lutea, and implantation sites.

Toxicokinetics

Blood samples from TK satellite animals were taken on PND 21, 31, and 70 from 3 animals/sex/group at 0, 0.5, 1, 3, 6, and 12 hrs (just prior to the second daily dose) after the first daily dose administration. Plasma levels of parent drug [deutetrabenazine (SD-809)] and the major active metabolites [d6 α-dihydrotetrabenazine (SD-948) and d6 β-dihydrotetrabenazine (SD-949)] were measured. Juvenile rats had much greater exposure to parent (SD-809) on PND 21 (10-fold higher) than at the end of weaning on PND 70 (similar to adult levels), greater effect in male rats. Metabolite levels (α+β-HTBZ) in male juvenile rats was similar across age range (PND 21-70), however in female juvenile rats levels of α+β-HTBZ were higher in younger rats (PND 21-31) compared to older (PND 70) and adult rats. The age-related differences in parent and metabolite plasma exposure may be related to age-related differences in metabolizing enzymes in rats (e.g., CYP2D6).

Table 6: Toxicokinetic parameters for SD-809 (deutetrabenazine) in juvenile rats

SD-809 Dose (mg/kg/dose)	Parameter	Male			Female		
		PND 21	PND 31	PND 70	PND 21	PND 31	PND 70
1.25	AUC_{last} (h*ng/mL)	38.0	0.232	1.01	32.7	2.50	2.91
	Dose Normalized AUC_{last}	15.2	0.0930	0.404	13.1	0.998	1.16
	C_{max} (ng/mL)	20.8	0.930	1.60	13.5	4.43	3.82
	Dose Normalized C_{max}	8.31	0.372	0.640	5.41	1.77	1.53
	T_{max} (h)	1	0.5	0.5	1	0.5	0.5
	$T_{1/2}$ (h)	NC	NC	NC	NC	NC	NC
	Accumulation Ratio	NA	0.00612	0.0266	NA	0.0763	0.0889
2.5	AUC_{last} (h*ng/mL)	63.2	0.946	2.35	71.9	1.77	3.04
	Dose Normalized AUC_{last}	12.6	0.189	0.471	14.4	0.354	0.608
	C_{max} (ng/mL)	31.5	1.78	2.24	36.3	3.22	2.35
	Dose Normalized C_{max}	6.30	0.355	0.448	7.26	0.644	0.471
	T_{max} (h)	0.5	0.5	0.5	0.5	0.5	0.5
	$T_{1/2}$ (h)	1.90	NC	NC	1.85	NC	NC
	Accumulation Ratio	NA	0.0150	0.0372	NA	0.0246	0.0423
5	AUC_{last} (h*ng/mL)	174	6.53	7.92	102	15.6	18.2
	Dose Normalized AUC_{last}	17.4	0.653	0.792	10.2	1.56	1.82
	C_{max} (ng/mL)	72.9	4.77	4.27	41.3	12.1	9.21
	Dose Normalized C_{max}	7.29	0.477	0.427	4.13	1.21	0.921
	T_{max} (h)	1	0.5	0.5	0.5	0.5	0.5
	$T_{1/2}$ (h)	NC	NR	NR	1.41	NC	0.934
	Accumulation Ratio	NA	0.0374	0.0454	NA	0.153	0.178

Note = Units for Dose Normalized AUC_{last} and Dose Normalized C_{max} are (h*ng/mL)/(SD-809 mg/kg/day) and (ng/mL)/(SD-809 mg/kg/day), respectively.
NC = Not calculable
NR = Not reportable, because plasma concentration time profiles failed to meet acceptance criteria listed in the definitions.
NA = Not applicable

[Table source: study no. SD-809-NC-055]

Table 7: Toxicokinetic parameters for SD-948 (d6-α-dihydrotetrabenazine) in juvenile rats

SD-809 Dose (mg/kg/dose)	Data	Male			Female		
		PND 21	PND 31	PND 70	PND 21	PND 31	PND 70
1.25	AUC_{last} (h*ng/mL)	119	135	180	114	139	27.8
	Dose Normalized AUC_{last}	47.8	53.8	71.9	45.7	55.5	11.1
	C_{max} (ng/mL)	21.6	22.7	32.7	17.9	28.8	4.65
	Dose Normalized C_{max}	8.65	9.08	13.1	7.15	11.5	1.86
	T_{max} (h)	1	0.5	0.5	1	1	3
	$T_{1/2}$ (h)	2.76	1.58	1.86	3.47	1.72	NC
	Accumulation Ratio	NA	1.13	1.50	NA	1.22	0.243
	Metabolite/Parent Ratio	3.15	579	178	3.49	55.6	9.55
2.5	AUC_{last} (h*ng/mL)	288	283	311	278	246	63.3
	Dose Normalized AUC_{last}	57.6	56.6	62.2	55.7	49.3	12.7
	C_{max} (ng/mL)	33.3	64.3	69.7	40.4	67.8	22.2
	Dose Normalized C_{max}	6.66	12.9	13.9	8.09	13.6	4.44
	T_{max} (h)	0.5	0.5	0.5	1	0.5	0.5
	$T_{1/2}$ (h)	2.34	2.08	2.35	2.41	2.07	1.94
	Accumulation Ratio	NA	0.983	1.08	NA	0.885	0.227
	Metabolite/Parent Ratio	4.56	299	132	3.87	139	20.8
5	AUC_{last} (h*ng/mL)	668	611	669	703	521	139
	Dose Normalized AUC_{last}	66.8	61.1	66.9	70.3	52.1	13.9
	C_{max} (ng/mL)	118	108	185	113	159	28.8
	Dose Normalized C_{max}	11.8	10.8	18.5	11.3	15.9	2.88
	T_{max} (h)	3	0.5	0.5	1	0.5	0.5
	$T_{1/2}$ (h)	NC	2.03	2.40	2.70	1.86	2.30
	Accumulation Ratio	NA	0.915	1.00	NA	0.742	0.197
	Metabolite/Parent Ratio	3.83	93.6	84.5	6.86	33.3	7.61

Note = Units for dose-normalized AUC_{last} and dose-normalized C_{max} are (h*ng/mL)/(SD-809 mg/kg/day) and (ng/mL)/(SD-809 mg/kg/day), respectively.
NC = Not calculable
NA = Not applicable
[Table source: study no. SD-809-NC-055]

Table 8: Toxicokinetic parameters for SD-949 (d6-β-dihydrotetrabenazine) in juvenile rats

SD-809 Dose (mg/kg/dose)	Data	Male			Female		
		PND 21	PND 31	PND 70	PND 21	PND 31	PND 7
1.25	AUC_{last} (h*ng/mL)	0.631	0.110	0.359	1.31	1.36	0.215
	Dose Normalized AUC_{last}	0.253	0.0439	0.143	0.523	0.544	0.086(
	C_{max} (ng/mL)	0.972	0.439	0.628	0.707	0.751	0.507
	Dose Normalized C_{max}	0.389	0.176	0.251	0.283	0.300	0.203
	T_{max} (h)	1	0.5	0.5	1	0.5	0.5
	$T_{1/2}$ (h)	NC	NC	NC	NC	NC	NC
	Accumulation Ratio	NA	0.174	0.568	NA	1.04	0.165
	Metabolite/Parent Ratio	0.0166	0.472	0.355	0.0399	0.545	0.073
2.5	AUC_{last} (h*ng/mL)	2.30	0.69	2.47	3.51	1.03	1.89
	Dose Normalized AUC_{last}	0.461	0.138	0.494	0.702	0.207	0.378
	C_{max} (ng/mL)	1.37	1.15	1.29	2.13	1.63	1.21
	Dose Normalized C_{max}	0.274	0.230	0.257	0.425	0.326	0.243
	T_{max} (h)	0.5	0.5	1	0.5	0.5	0.5
	$T_{1/2}$ (h)	NC	NC	NC	NC	NC	NC
	Accumulation Ratio	NA	0.300	1.07	NA	0.294	0.538
	Metabolite/Parent Ratio	0.0364	0.730	1.05	0.0488	0.584	0.621
5	AUC_{last} (h*ng/mL)	14.0	7.24	6.75	11.5	7.77	8.14
	Dose Normalized AUC_{last}	1.40	0.724	0.675	1.15	0.777	0.814
	C_{max} (ng/mL)	4.83	2.83	3.83	3.87	5.47	4.37
	Dose Normalized C_{max}	0.483	0.283	0.383	0.387	0.547	0.437
	T_{max} (h)	1	0.5	0.5	0.5	0.5	0.5
	$T_{1/2}$ (h)	NC	1.57	NC	1.73	NC	NC
	Accumulation Ratio	NA	0.516	0.482	NA	0.676	0.708
	Metabolite/Parent Ratio	0.0804	1.11	0.853	0.112	0.497	0.447

Note = Units for Dose Normalized AUC_{last} and Dose Normalized C_{max} are (h*ng/mL)/(SD-809 mg/kg/day) and (ng/mL)/(SD-809 mg/kg/day), respectively.
NC = Not calculable
NA = Not applicable

[Table source: study no. SD-809-NC-055]

6 Clinical Pharmacology

6.1. Executive Summary

In this efficacy supplement, the Applicant submitted an open-label pilot phase 1b clinical study (SD-809-C-17) in adolescent patients (12 to 18 years) with Tourette Syndrome (TS) and three phase 2/3 clinical studies (TV50717-CNS 30046, TV50717-CNS 30060, and TV50717-CNS-30047) in children (6 to 11 years) and adolescent (12 to 16 years) patients with motor and phonic tics associated with TS. The rich pharmacokinetic (PK) samples were collected in study SD-809-C-17 and the sparse PK samples were collected in studies TV50717-CNS 30046 and TV50717-CNS 30060.

This review is focused on evaluating the PK of deutetrabenazine and its active metabolites, alpha-dihydrodeutetrabenazine (α-HTBZ) and β-dihydrodeutetrabenazine (β-HTBZ) in children (6 to 11 years) and adolescents using population PK approach.

6.2. Summary of Clinical Pharmacology Assessment

Population PK analyses suggest that the dose-normalized systemic exposures (Cmax-ss and AUCss) to deutetrabenazine and its active metabolites (α-HTBZ and β-HTBZ) are relatively similar across the weight groups, 20-30 kg, 30-40 kg, and greater than 40 kg in children (6 to 11 years old) and adolescent patients with tics associated TS. (Please refer to the Appendix, Section 14.4 of this review for additional information.)

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant conducted four studies in pediatric patients with TS. Study SD-809-C-17 (henceforth referred to as C-17) was an open-label pilot study that evaluated the safety and tolerability of deutetrabenazine in adolescent patients (ages 12 to 18 years) with TS. Studies TEV-50717-CNS-30046 and TEV-50717-CNS-30060 (30046 and 30060) were randomized, double-blind, placebo-controlled efficacy and safety studies in pediatric patients ages 6 to 16 years with TS. Study TEV-50717-CNS-30047 (30047) was an open-label, long-term safety extension study that enrolled patients who completed Studies 30046 and 30060.

Table 9: Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
TEV-50717-CNS-30046	Double-blind, placebo-controlled, flexible-dose efficacy and safety study Randomization 1:1 (drug:placebo)	Starting dose 6 mg/day orally, titrated up to 48 mg/day based on weight, CYP2D6 impairment status, efficacy, and tolerability	Primary endpoint: Yale Global Tic Severity Scale – Total Tic Score (YGTSS-TTS)	7-week titration 5-week maintenance 1-week follow-up	119 enrolled	Patients ages 6 to 16 years motor or phonic tics associated with TS	36 centers; 6 countries
TEV-50717-CNS-30060	Double-blind, placebo-controlled, fixed-dose efficacy and safety study Randomization 1:1:1 (high-dose: low-dose: placebo)	Doses titrated to fixed-dose based on patient weight and CYP2D6 status. Low-dose (oral): 6-12 mg/day to 6-36 mg/day High-dose (oral): 6-12 mg/day to 12-48 mg/day	YGTSS-TTS	4-week dose escalation 4-week maintenance 1-week follow-up	158 enrolled	Patients ages 6 to 16 years motor or phonic tics associated with TS	52 centers; 10 countries
Studies to Support Safety							
TEV-50717-CNS-30047	Open-label safety extension, including randomized withdrawal phase	6 mg/day to 48 mg/day orally	Safety endpoints; YGTSS-TTS was a secondary endpoint in the randomized withdrawal period	56 weeks, including 2-week randomized withdrawal period	228 enrolled	Patients who completed 30046 or 30060. No C-17 patients enrolled.	77 centers; 15 countries
SD-809-C-17	Open-label PK, safety,	Starting dose 6mg orally once daily, titrated weekly based on	Safety endpoints	8-week treatment	23 enrolled	Patients ages 12 to 18	9 centers in the United

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	tolerability, preliminary efficacy study	safety and efficacy to a maximum of 36 mg/day		1-week follow-up		years with motor or phonic tics associated with TS	States

[Table source: reviewer created]

7.2. Review Strategy

The assessment of efficacy is based on Studies 30046 and 30060, the randomized, double-blind placebo-controlled studies in pediatric patients with TS. The assessment of safety focused primarily on those two studies, but also considered data from the open-label safety and tolerability study (C-17) and the long-term safety study (30047).

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. TV50717-CNS-30046 and TV50717-CNS-30060

Trial Design - 30046

30046 was a randomized, double-blind, placebo-controlled, flexible-dose study to evaluate the efficacy and safety of TEV-50717 (deutetrabenazine) for treatment of motor and phonic tics associated with TS. Patients ages 6 to 6 years weighing at least 20 kg who met DSM-5 criteria for TS were eligible to enroll. A total tic score (TTS) of 20 or higher on the YGTSS was required.

Notable exclusion criteria included:

- Presence of another neurological disorder that could obscure the evaluation of tics
- Presence of bipolar disorder, schizophrenia, or other psychotic disorder
- Clinically significant depression
- Suicidal intent or behavior within 2 years of screening
- Clinically significant obsessive-compulsive disorder (OCD) that was the primary cause of impairment
- CBIT or cognitive behavioral therapy for OCD within 4 weeks of screening
- Prolonged QT interval, hepatic impairment, renal impairment, or unstable/serious medical illness at baseline

Prohibited medications included depot and oral neuroleptics, botulinum toxin, tetrabenazine, cannabidiol oil, valbenazine, reserpine, typical and atypical antipsychotics, metoclopramide, levodopa, and dopamine agonists.

Patients were randomized (1:1) to receive TEV-50717 or placebo. Patients were stratified by age at baseline (6 to 11 years and 12 to 16 years). TEV-50717 was administered at a starting dose of 6 mg once daily. The maximum daily dose was determined by weight and CYP2D6 impairment status at baseline (**Table 10**).

Table 10: Dosing by Weight and CYP2D6 Status, Study 30046

	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**
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.
[Source: Clinical Study Report Synopsis, Study 30046, page 3]

Patients underwent 7 weeks of dose titration and 5 weeks of maintenance therapy.

Trial Design - 30060

Study 30060 was a randomized, double-blind, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of TEV-50717 (deutetrabenazine) for treatment of motor and phonic tics associated with TS. The inclusion and exclusion criteria were similar to those of Study 30046.

Patients were randomized (1:1:1) to receive high-dose TEV-50717, low-dose TEV-50717, or placebo. TEV-50717 was administered at a starting dose of 6 mg once daily. The maximum daily dose was determined by weight and CYP2D6 impairment status at baseline (**Table 11**).

Table 11: Dosing by Weight and CYP2D6 Impairment Status, Study 30060

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

[Source: Clinical Study Report, Study 30060, Table 2, page 38]

Patients underwent 4 weeks of dose escalation and 4 weeks of maintenance therapy.

Study Endpoints

The primary efficacy endpoint in both studies was the change in YGTSS-TSS from baseline to the end of treatment (Week 12 for Study 30046 and Week 8 for Study 30060).

The secondary efficacy endpoints in the studies were:

- Change from baseline to end of treatment on the Tourette Syndrome Clinical Global Impression (TS-CGI)
- Change from baseline to end of treatment on the Tourette Syndrome Patient Global Impression of Improvement (TS-PGII)
- Change from baseline to end of treatment on the Gilles de la Tourette Syndrome Quality of Life Activities of Daily Living (C&A-GTS-QOL ADL) subscale score

Statistical Analysis Plan

Studies 30046 and 30060 were conducted to investigate the potential use of deutetrabenazine in the treatment of tics associated with Tourette syndrome in children and adolescents ages 6 to 16 years. To obtain the needed pediatric information on TEV-50717, the FDA issued a formal Written Request (WR) on January 8, 2020. Subsequently, the Sponsor conducted the clinical studies as requested by the FDA. Neither study demonstrated efficacy.

Study 30046
The Applicant planned the study such that approximately 58 patients per arm would enable a power of at least 90% to detect a treatment effect when the TEV-50717 arm was compared to placebo (assuming a difference of 6.0 in the change from baseline to week 12 in the TTS and a standard deviation (SD) of 9.5 in each arm) with a 2-sided type I error rate of 5% after accounting for potential dropouts. The study plan was amended, using external phase 2b data, from the original assumption of 68% standardized effect to 63% (=0.60/9.5).

The Applicant analyzed the change from baseline in YGTSS-TTS total score at Week 12 using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included treatment, week and treatment-by-week interaction as fixed effects as fixed effects; baseline TTS, region and age group at baseline as covariates. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. A fixed sequence testing approach was applied to control the experiment-wise type I error at 5% in the order as listed in Study Endpoints above.

Study 30060
The Applicant planned the study with 150 patients such that approximately 50 patients per arm would enable a power of at least 90% to detect a treatment effect, assuming a treatment difference 6.5 points in the change from baseline to week 8 in TTS when the TEV-50717 high-dose arm was compared to placebo, and SD of 9.5, and a 2-sided type I error rate of 5% after accounting for potential dropouts. The study protocol was amended to increase the sample size although it was decided, based on external data, to amend it back to the original sample size.

The Applicant analyzed the change from baseline in YGTSS-TTS total score at Week 8 using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included treatment, week and treatment-by-week interaction as fixed effects as fixed effects; baseline TTS, region and age group at baseline as covariates. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Following the testing of YGTSS-TTS (high dose TEV-50717 versus placebo), the secondary endpoints were tested alternately between high-dose/low-dose using a fixed sequence testing approachto control the experiment-wise type I error at 5%.

Protocol Amendments

There was one statistically-relevant protocol amendment (March 25, 2019) in Study 30046 where the treatment effect assumption in the sample size calculation was re-evaluated based on external data (valbenazine phase 2 study results; efficacy of TEV-50717 in treatment of HD and TD; and Abilify phase 3 data).

There were two protocol amendments related to statistics in Study 30060. In the first amendment (March 25, 2019), a decision was made to increase the sample size based on external data (valbenazine phase 2 study results, efficacy of TEV-50717 in the treatment of HD and TD, and ABILIFY phase 3 data). But due to substantially lower efficacy in the Abilify phase 3 study, the previous decision was revised and in the second amendment (May 5, 2019), to revert the sample size back to the original assumed size before the first amendment was issued.

Clinical Reviewer Comment: *Studies 30046 and 30060 were adequate and well-controlled studies* (b) (4) *The inclusion and exclusion criteria were appropriate for ensuring that a clinically relevant population was enrolled. The primary efficacy endpoint has been validated for use in this population and captured clinically meaningful concepts.*

8.1.2. Study Results

Compliance with Good Clinical Practices

A statement of Good Clinical Practice is included in the final clinical study reports for the two efficacy and safety studies (30046 and 30060), the open-label safety extension (30047), and the pilot open-label safety and tolerability study (C-17).

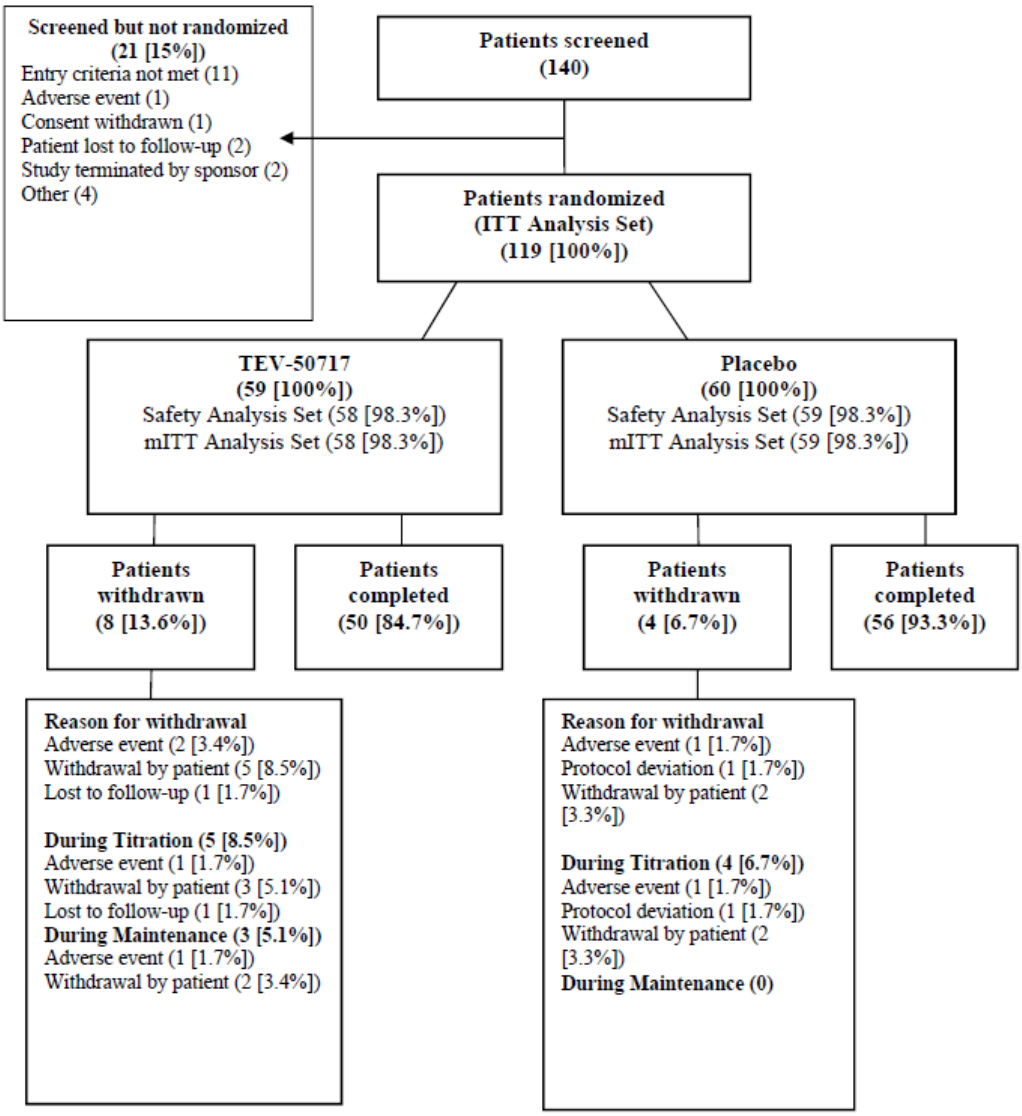
Financial Disclosure
The Applicant has adequately disclosed financial interests and arrangements with clinical investigators. The Applicant did not disclose any interests or arrangements which raised questions about the integrity of the study data.

Patient Disposition

Study 30046

Figure 2 summarizes patient disposition in Study 30046. The most common reason for study discontinuation in patients receiving TEV-50717 was withdrawal by patient. A larger percentage of patients in the TEV-50717 group compared with the placebo group withdrew because of adverse events (3.4% and 1.7% respectively).

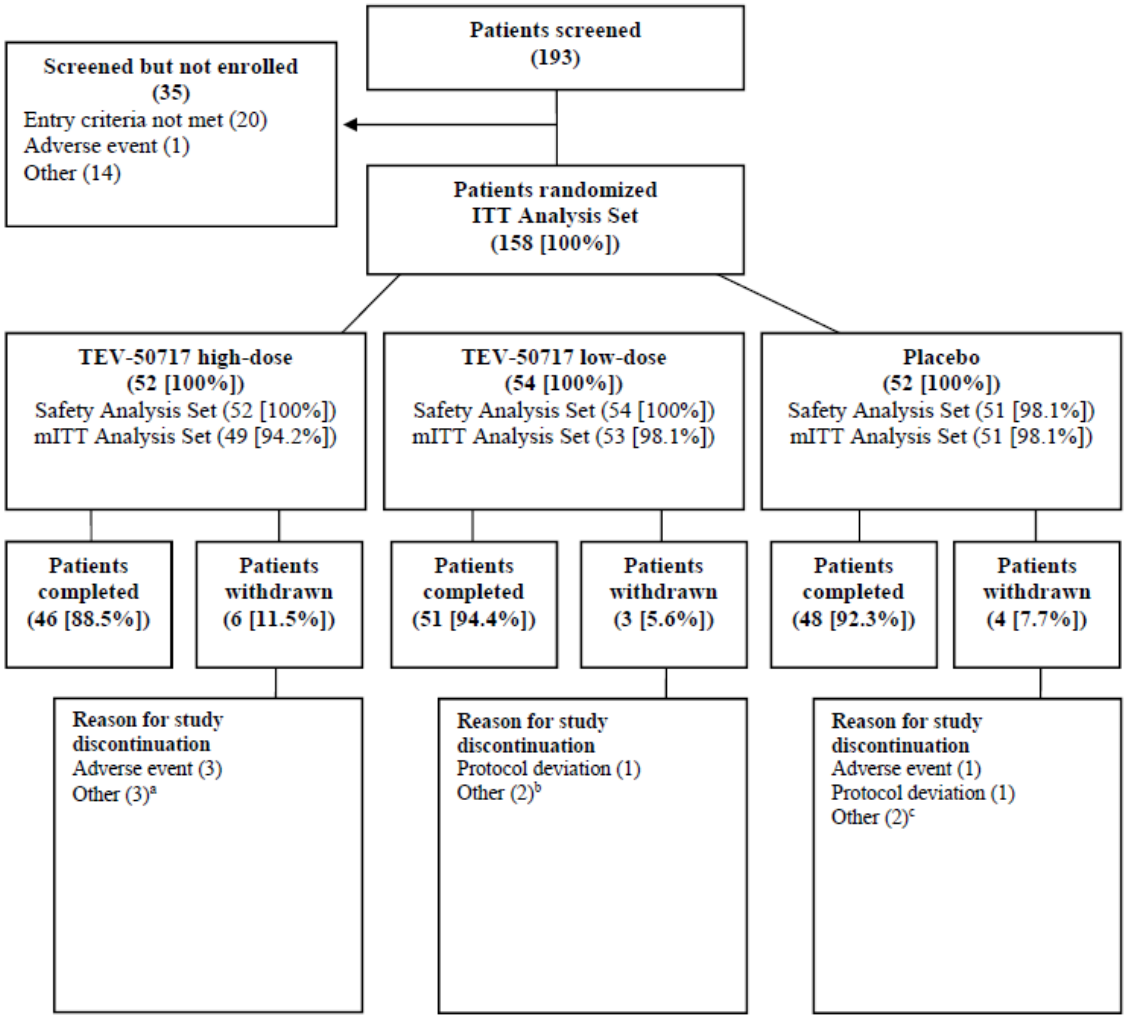
Figure 2: Patient Disposition, Study 30046



[Source: Clinical Study Report, Study 30046, Figure 2, page 75]
ITT = intent-to-treat
mITT = modified intent-to-treat

Figure 3 summarizes patient disposition in Study 30060. Study completion rates were similar in the low-dose TEV-50717 group (94.4%) and the placebo group (92.3%) and lower in the high-dose group TEV-50717 (88.5%). Patients in the high-dose group TEV-50717 group were more likely to withdraw from the study because of adverse events.

Figure 3: Patient Disposition, Study 30060



ITT = intent-to-treat
mITT = modified intent-to-treat
[Source: Clinical Study Report, Study 30060, Figure 2, page 77]

Protocol Violations/Deviations

In Study 30046, a higher proportion of patients in the ITT analysis set for the TEV-50717 group (12/59, 20%) had major protocol deviations related to dosing compared to patients in the placebo group (3/60, 5%). Most of these dosing errors related to mistimed starts of assigned blister packs or use of the incorrect blister pack during the titration period. No patients with dosing errors reported adverse events that led to drug discontinuation. No major protocol deviations related to enrollment criteria occurred in Study 30046. The frequency of major protocol violations related to laboratory assessments and nonadherence were similar in the TEV-50717 and placebo arms. In Study 30060, the frequency of major protocol deviations related to enrollment criteria, laboratory assessments, dosing, and nonadherence were comparable in the TEV-50717 arms and the placebo arm.

Table of Demographic Characteristics

The demographic characteristics of patients in Studies 30046 and 30060 are summarized in **Table 12** and **Table 13**. The treatment groups in each study were demographically similar. The population included in the completed studies was approximately 86% White, 3% Black/African American, 3% Asian, 2% Native American, 2% Multiple race, and 4% Other race. Black/African-American representation was higher (5%) in Study 30046, which enrolled a majority of patients from North American sites.

Prevalence of TS among Hispanic and Black children has been reported to be half that observed among White children. However, it is unclear whether these racial and ethnic differences represent under-reporting in racial minority groups or true differences in prevalence (Bitsko et al. 2014). In response to an information request from the Agency, the Applicant provided additional information about its efforts to enroll an adequate representation of children of ethnic and racial minorities. Strategies to recruit a representative population included: selection of diverse geographic regions in the United States and outside of the United States; inclusion of sites in urban areas; and availability of a Spanish consent form in the United States.

Table 12: Demographic characteristics of the primary efficacy analysis, Study 30046

Demographic Parameters	**Control Group** (N=60) n (%)	**TEV-50717** (N=59) n (%)	**Total** (N=119) n (%)
Sex			
Male	51 (85)	53 (89.8)	104 (87.4)
Female	9 (15)	6 (10.2)	15 (12.6)
Age			
Mean years (SD)	11.5	11.5	11.5
Median (years)	11	11	22
Min, max (years)	6, 16	6, 16	6, 16
Age Group			
6 to 11 years	31 (51.7)	30 (50.8)	61 (51.3)
12 to 16 years	29 (48.3)	29 (49.2)	58 (48.7)
Race			
White	53 (88.3)	49 (83.1)	102 (85.7)
Black or African American	3 (5)	3 (5.1)	6 (5)
Asian	1 (1.7)	1 (1.7)	2 (1.7)
Native American	0	1 (1.7)	1 (0.8)
Multiple	1 (1.7)	3 (5.1)	4 (3.4)
Other[1]	2 (3.3)	2 (3.4)	4 (3.4)
Ethnicity			
Hispanic or Latino	8 (13.3)	5 (8.5)	13 (10.9)
Not Hispanic or Latino	50 (83.3)	51 (86.4)	101 (84.9)
Unknown	2 (3.3)	3 (5.1)	5 (4.2)
Region (optional)			
United States	30 (50)	36 (61)	66 (55.5)
Rest of the World	30 (50)	23 (39)	53 (44.5)

[1] Data on race and/or ethnicity were not collected in certain countries because of local regulations.

[Source: Adapted from Clinical Study Report, Study 30046, Table 7, page 78]

Table 13: Demographic characteristics of the primary efficacy analysis, Study 30060

Demographic Parameters	**Control Group** (N=52) n (%)	**TEV-50717 (low dose)** (N=54) n (%)	**TEV-50717 (high dose)** (N=52) n (%)	**Total** (N=158) n (%)
Sex				
Male	40 (76.9)	42 (77.8)	37 (71.2)	119 (75.3)
Female	12 (23.1)	12 (22.2)	15 (28.8)	39 (24.7)
Age				
Mean years (SD)	11.8	11.7	11.7	11.7
Median (years)	12	12	12	12
Min, max (years)	7, 16	6, 16	6,16	6, 16
Age Group				
6 to 11 years	21 (40.4)	22 (40.7)	21 (40.4)	64 (40.5)
12 to 16 years	31 (59.6)	32 (59.3)	31 (59.6)	94 (59.5)
Race				
White	39 (75)	48 (88.9)	48 (92.3)	135 (85.4)
Black or African American	0	1 (1.9)	0	1 (0.6)
Asian	4 (7.7)	3 (5.6)	0	7 (4.4)
Native American	2 (3.8)	1 (1.9)	1 (1.9)	4 (2.5)
Multiple	2 (3.8)	0	0	2 (1.3)
Other[1]	5 (9.6)	1 (1.9)	3 (5.8)	9 (5.7)
Ethnicity				
Hispanic or Latino	15 (28.8)	9 (16.7)	8 (15.4)	32 (20.3)
Not Hispanic or Latino	37 (71.2)	45 (83.3)	43 (82.7)	125 (79.1)
Unknown	0	0	1 (1.9)	1 (0.6)
Region (optional)				
United States	14 (26.9)	13 (24.1)	13 (25)	40 (25.3)
Rest of the World	38 (73.1)	41 (75.9)	39 (75)	118 (74.7)

[1] Data on race and/or ethnicity were not collected in certain countries because of local regulations.
[Source: Clinical Study Report, Study 30060, Table 10.1.2.1, page 80]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The treatment groups in Study 30046 were comparable in terms of baseline clinical characteristics including the mean time to TS diagnosis, the mean baseline YGTSS-TTS score, mean weight, mean height, mean body mass index (BMI), proportion of patients with CYP2D6 impairment, and proportion of patients using a strong CYP2D6 inhibitor. A greater proportion of patients in the TEV-50717 group than in the placebo group had a prior history of psychiatric disorders (81.4% and 66.7%, respectively). The prevalence of OCD, depression, and anxiety was similar in the two treatment groups; however, a higher proportion of patients in the TEV-50717 had a diagnosis of ADHD (62.7%) than in the placebo group (51.7%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In Study 30046, five patients in the TEV-50717 group (8.6%) and one patient in the placebo

group (1.7%) reported less than 80% compliance with study drug administration. No patients reported >105% compliance with study drug administration. At baseline, a higher proportion of patients in the TEV-50717 group (75.9%) were taking concomitant medications at baseline and continued them during the study than in the placebo group (55.9%). In the TEV-50717 group, 53.4% of patients were prescribed ADHD medications (including stimulants, alpha agonists, atomoxetine, and cognitive enhancers), compared to 42.4% of patients in the placebo group. 24.1% of patients treated with TEV-50717 were concomitantly prescribed medications for depression, compared with 16.9% of patients on placebo. No patients in the TEV-50717 group were prescribed medications for anxiety, compared to 5.1% of patients in the placebo group.

In Study 30060, one patient in each of the TEV-50717 treatment groups reported less than 80% compliance with study drug administration. One patient the low-dose TEV-50717 group reported > 105% compliance. Patients in the high-dose TEV-50717 group were more likely to continue baseline concomitant medications (55.8%) than patients in the low-dose group (46.3%) or the placebo group (35.3%). The proportion of patients taking medications for ADHD was similar in the high-dose, low-dose, and placebo groups (25%, 22.2%, and 23.5%, respectively). The proportion of patients taking medications for anxiety was higher in the TEV-50717 high- and low-dose groups (15.4% and 13%) than in the placebo group (5.9%). The proportion of patients prescribed medications for anxiety was similar across treatment groups.

Few patients during the studies changed or stopped ADHD or antidepressant medications during the study.

Clinical Reviewer Comment*: The higher rate of co-occurring psychiatric conditions in the deutetrabenazine treatment groups was largely attributable to a greater percentage of patients with ADHD. Patients in the TEV-50717 treatment groups were somewhat more likely to be prescribed concomitant medications at baseline, including treatments for ADHD, depression, and anxiety. Concomitant use of alpha agonists for ADHD, which have been used as off-label treatments for TS, was similar in the drug and placebo groups in both studies. Stimulant medications were previously suspected to unmask or worsen tics. More recent evidence suggests that stimulants are unlikely to exacerbate tics in most patients (Osland et al. 2018) and so slight disparities in the frequency of stimulant use in the treatment groups likely did not meaningfully impact the study results. The baseline disease severity and disease characteristics were similar in the TEV-50717 and placebo groups. In general, despite the population differences described above, the drug and placebo groups were similar enough for comparison in the submitted studies.*

Efficacy Results – Primary Endpoint

Study 30046
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 (Table 14). At Week 12, the TEV-50717 had a difference of -0.7 points from placebo and the study failed to meet the primary objective (95% CI: -4.1 to 2.8; p=0.692.

Table 14: Primary Efficacy Analysis: YGTSS-TTS Total Score Change from Baseline at Week 12 in ITT, Study 30046

	TEV-50717 (N=58)	Placebo (N=59)
Mean Baseline Score (SD)	31.7 (5.85)	33.1 (5.91)
Mean Score at Week 12 (SD)	22.0 (11.04)	23.9 (9.06)
n	51	56
LS Mean Change from Baseline (SE)	-9.1 (1.28)	-8.4 (1.25)
95% CI	(-4.1, 2.8)	
p-value[2]	0.69	

Abbreviations: N = number of patients in primary efficacy analysis set; n= number of patients remaining at Week 12; CI = confidence interval, not adjusted for multiplicity; LS = leastsquares; SD = standard deviation; SE = standard error
[1] Difference (drug minus placebo) in least-squares mean change from baseline computed using mixed-effect model repeated measure method (MMRM)
[2] Multiplicity adjustment: fixed sequence testing
[Source: Tables 14.2 and 14.2.1.1.1, Clinical Study Report, pages 283-5]

Study 30060

The primary efficacy endpoint, the change in the YGTSS-TTS from baseline to the end of therapy at week 8, did not show a statistically significant difference between TEV-50717 high-dose group and placebo (Table 15), with a treatment effect of -0.8 (95% CI: -3.9 to 2.3; p=0.600. The result for the low dose was also not statistically significant.

Table 15: Primary Efficacy Analysis: YGTSS-TTS Total Score Change from Baseline at Week 8 in mITT, Study 30060

	TEV-50717 high-dose (N=40)	TEV-50717 low-dose (N=53)	Placebo (N=51)
Mean Baseline Score (SD)	33.9 (5.98)	33.1 (7.01)	35.2 (5.28)
Mean Score at Week 8 (SD)	25.6 (9.85)	27.3 (9.12)	27.2 (9.13)
n	48	51	49
LS Mean Change from Baseline (SE)	-7.8 (1.24)	-5.9 (1.18)	-7.0 (1.16)
95% CI	(-3.9, 2.3)	(-1.9, 4.2)	
p-value [2]	0.6	0.474	

Abbreviations: N = number of patients in primary efficacy analysis set; n= number of patients remaining at Week 8; CI = confidence interval, not adjusted for multiplicity; LS = least-squares; SD = standard deviation; SE = standard error
[1] Difference (drug minus placebo) in least-squares mean change from baseline computed using mixed-effect model repeated measure method (MMRM)
[2] Multiplicity adjustment: fixed sequence testing
[Source: Tables 14.2.1.1.1 and 14.2.1.2.1, Clinical Study Report, pages 271 and 273]

Data Quality and Integrity

The quality and integrity of the submitted datasets were adequate for full review and analysis of the study data.

Efficacy Results – Secondary and other relevant endpoints

Study 30046
Because the hierarchical hypothesis testing strategy, testing was stopped once the primary hypothesis step and all the secondary endpoints were considered exploratory. The results of secondary efficacy analyses did not show nominal significance.
Study 30060
The fixed sequence testing stopped once the primary hypothesis step failed to meet the primary objective. None of the secondary endpoints were nominally significant.

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Secondary endpoints were not formally tested.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

As noted above, neither Study 30046 nor 30060 detected a treatment effect.

8.1.4. Integrated Assessment of Effectiveness

Two adequate and well-controlled efficacy and safety studies of deutetrabenazine failed to demonstrate substantial evidence of effectiveness for the treatment of tics associated with TS in patients 6 to 16 years of age.

8.2. Review of Safety

8.2.1. Safety Review Approach

The two randomized, placebo-controlled efficacy and safety studies (30046 and 30060) were the primary focus of the safety review. Clinical Study Reports (CSRs), adverse events, laboratory assessments, vital signs, electrocardiograms, and data from Columbia Suicide Severity Rating Scale (C-SSRS) and Children's Depression Inventory (CDI-2) were analyzed. Safety data from 30047, the long-term safety extension, and from C-17, an open-label pilot study were also considered.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 1467 individuals have been exposed to deutetrabenazine across development programs, including 282 patients with TS, 390 patients with TD, 121 patients with chorea associated with HD, and 674 healthy adult volunteers.

In Studies 30046 and 30060, the mean duration of exposure was 62.8 days in patients randomized to TEV-50717 treatment groups. Study 30047, the long-term safety study, was terminated early because the two parent studies failed to demonstrate a treatment effect on the primary efficacy endpoint. Nonetheless, 110 patients (48.5%) in 30047 were exposed to deutetrabenazine for > 28 to ≤ 52 weeks. The mean duration of exposure during open-label treatment in 30047 was 27.7 weeks.

Adequacy of the safety database:

The safety population for the TS development program included all patients who were exposed to at least one dose of study medication (**Table 16**).

Table 16: Safety Population, Size and Denominators

Clinical Trial Groups	TEV-50717 (n=282)	Placebo (n=14)
Controlled trials conducted (b) (4) (b) (4)	164	14
All other than controlled trials conducted (b) (4)	118*	0

* 95 patients who received placebo in Studies 30046 and 30060 were treated with TEV-50717 in 30047 (open-label extension). 23 patients were exposed to open-label TEV-50717 in Study C-17.
[Source: Reviewer created]

As noted above, the population in the submitted studies appears reflect the clinical population of pediatric patients seeking treatment for TS in terms of disease characteristics and demographics, though racial and ethnic minorities may be underrepresented in the clinical population. The size of the safety database was adequate for a meaningful safety analysis in this orphan-designated development program.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity or submission quality were identified. The submitted datasets were complete and the data were presented in an organized manner that allowed for substantive review.

Categorization of Adverse Events

Adverse events in Studies 30046, 30060, and 30047 were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1; adverse events in Study C-17 were coded using Version 17.0. I reviewed the Applicant's definition of adverse event and the Applicant's methods for determining the severity and seriousness of an adverse event and its relationship to the investigational medical product. Adverse events in the submitted clinical trials were categorized in a way that is typical of psychiatric studies. The Applicant used standardized MedDRA queries (SMQs) to group adverse events related to suicide/self-injury, depression, and Parkinson-like events.

Routine Clinical Tests

Routine clinical tests in Studies 30046, 30060, 30047, and C-17 included serum chemistry, complete blood count with differential, serum/urine pregnancy tests, vital signs, physical examinations (including neurological examination), electrocardiograms, and 2D6 genotyping. Clinical outcome assessments included the Columbia Suicide Severity Rating Scale (C-SSRS), the Children's Depression Inventory (CDI-2), and the Yale Brown Obsessive Compulsive Scale (Y-BOCS). The scope of the clinical assessments was appropriate given deutetrabenazine's mechanism of action, the known safety profile in previously studied adult populations, and common comorbidities in pediatric patients with TS.

8.2.4. Safety Results

Deaths

No deaths occurred in the pediatric TS development program.

Serious Adverse Events

No serious adverse events (SAEs) were reported in Studies C-17 or 30046.

One patient in Study 30060 (Patient (b) (6)) reported two SAEs. This patient developed worsening of ADHD symptoms and tics after discontinuing atomoxetine. The patient was hospitalized to restart atomoxetine, recovered, completed the study, and rolled into Study 30047.

Four SAEs were reported in three patients in Study 30047:

- Patient (b) (6) – self-injurious behavior
- Patient (b) (6) – depressed mood and suicidal behavior. These events began 12 days after the last dose of the drug per the Applicant's exposure data.
- Patient (b) (6) – abdominal pain upper

Clinical Reviewer Comment: *Serious adverse events were uncommon in the pediatric TS development program and were not suggestive of any unexpected safety signals.*

Dropouts and/or Discontinuations Due to Adverse Effects

In Study 30046, one patient in the TEV-50717 group and one patient in the placebo group discontinued study drug because of adverse events. In Study 30060, three patients receiving high-dose TEV-50717 and one patient receiving placebo discontinued study drug because of adverse events (no patients in the low-dose TEV-50717 group discontinued for this reason).

The four patients who discontinued TEV-50717 because of adverse events in Studies 30046 and 30060 reported the following events: restlessness, discomfort, fatigue, and weight increased; dystonia; abdominal pain and nausea; and anxiety and hallucinations. One patient who received placebo discontinued because of adverse events of abnormal behavior, aggression, anxiety, and depressed mood. Another patient treated with placebo discontinued because of intentional self-injury and suicidal ideation.

In Study 30047, 21 patients had at least one adverse event that led to discontinuation. The following adverse events led to discontinuation in more than one patient: depressed mood (3 patients), tic (3 patients); and weight increased (2 patients).

Clinical Reviewer Comment: *Adverse events leading to discontinuation were uncommon in the pediatric TS development program and no unifying pattern was evident.*

Significant Adverse Events

In Study 30046, the flexible-dose study, patients who were treated with TEV-50717 were more likely than patients treated with placebo to undergo dose reduction because of adverse events (**Table 17**). Fatigue was the only adverse event leading to dose reduction that was reported in more than one patient.

Table 17: Adverse Events Leading to Dose Reduction, Study 30046

System Organ Class Preferred Term[a]	Number (%) of Patients		
	TEV-50717 (N=58)	Placebo (N=59)	Total (N=117)
Patients with at least 1 TEAE leading to dose reduction	**7 (12.1)**	**1 (1.7)**	**8 (6.8)**
Nervous system disorders	4 (6.9)	1 (1.7)	5 (4.3)
Ataxia	1 (1.7)	0	1 (0.9)
Hypersomnia	1 (1.7)	0	1 (0.9)
Migraine	1 (1.7)	0	1 (0.9)
Sedation	1 (1.7)	0	1 (0.9)
Somnolence	1 (1.7)	0	1 (0.9)
Headache	0	1 (1.7)	1 (0.9)
General disorders and administration site conditions	2 (3.4)	1 (1.7)	3 (2.6)
Fatigue	2 (3.4)	1 (1.7)	3 (2.6)
Psychiatric disorders	1 (1.7)	0	1 (0.9)
Irritability	1 (1.7)	0	1 (0.9)
Skin and subcutaneous tissue disorders	1 (1.7)	0	1 (0.9)
Hyperhidrosis	1 (1.7)	0	1 (0.9)
Gastrointestinal disorders	0	1 (1.7)	1 (0.9)
Nausea	0	1 (1.7)	1 (0.9)
Vomiting	0	1 (1.7)	1 (0.9)

[a]Adverse events were classified by system organ class and preferred term using MedDRA version 22.1. Patients who experienced the same coded event more than once were counted only 1 time per preferred term and 1 time per system organ class.
MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
[Source: Applicant's Integrated Summary of Safety, Table 26, page 122]

In Study 30060, the Investigator was permitted to perform a single dose reduction of 6 mg. Three patients in the high dose TEV-50717 group had the following adverse events leading to dose reduction: vomiting, dizziness, fatigue, and somnolence; somnolence; and disturbance of attention.

Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported treatment-emergent adverse events (TEAEs) for Study 30046 and Study 30060 are presented in Table 18 and Table 19, respectively. In the fixed-dose study (30060), adverse events were generally more common in the high-dose group than in the low-dose group.

Table 18: Adverse Reactions Occurring in More than One TEV-50717-Treated Patient and More Frequently than in Placebo-Treated Patients, Study 30046

MedDRA Preferred Term	Placebo N=58	% Placebo	TEV-50717 N=59	% TEV-50717
Headache	6	10%	8	14%
Somnolence	1	2%	8	14%
Fatigue	3	5%	7	12%
Weight increased	1	2%	7	12%
Diarrhea	1	2%	4	7%
Enuresis	0	0%	4	7%
Increased appetite	1	2%	3	5%
Insomnia	1	2%	3	5%
Pyrexia	2	3%	3	5%
Gastroenteritis	1	2%	2	3%
Hyperhidrosis	0	0%	2	3%
Irritability	0	0%	2	3%
Rhinorrhea	1	2%	2	3%
Tremor	0	0%	2	3%

*Grouped Term
Headache – headache, migraine, migraine with aura
Somnolence – somnolence, sedation, hypersomnia
Anxiety - anxiety, panic attack
Insomnia - initial insomnia, insomnia, middle insomnia
Gastroenteritis - gastroenteritis, gastroenteritis viral
[Source: Reviewer created from adae.xpt]

Table 19: Adverse Reactions Occurring in More than One Patient in any TEV-50717 Dose Group and More Frequently than in Placebo-Treated Patients, Study 30060

MedDRA Preferred Term	Placebo N=51	% Placebo	TEV-50717 Low-Dose N=54	% Low-Dose	TEV-50717 High-Dose N=52	% High-Dose
Somnolence*	1	2%	2	4%	8	15%
Upper Respiratory Infection*	3	6%	3	6%	7	13%
Headache*	4	8%	8	15%	6	12%
Fatigue		0%	1	2%	5	10%
Abdominal pain*	1	2%	1	2%	4	8%
Increased appetite	0	0%	1	2%	4	8%
Tic	1	2%		0%	3	6%
Nausea	0	0%	3	6%	2	4%
Irritability	1	2%	2	4%	2	4%
Cough	0	0%	1	2%	2	4%
Anxiety*	0	0%	0	0%	2	4%
Agitation*	0	0%	0	0%	2	4%
Restlessness	0	0%	0	0%	2	4%
Pain in extremity	3	6%	0	0%	2	4%
Abnormal weight gain	0	0%	0	0%	2	4%
Oropharyngeal pain	1	2%	2	4%	1	2%
Epistaxis	1	2%	2	4%	1	2%

*Grouped Term
Somnolence - somnolence, sedation, hypersomnia
Upper Respiratory Infection - upper respiratory infection, nasopharyngitis, viral upper respiratory tract infection, pharyngitis, pharyngitis streptococcal
Headache - headache, migraine, migraine with aura
Abdominal Pain - abdominal pain upper, abdominal discomfort, abdominal pain
Anxiety - anxiety, panic attack
Agitation - anger, agitation, aggression
[Source: Reviewer created from adae.xpt]

In a pooled dataset of patients in both studies, adverse events occurring in ≥ 5% of patients in the TEV-50717 treatment groups and more frequently in the placebo group were headache (13% of TEV-50517 treatment group and 9% of placebo group), somnolence (11% and 2%), fatigue (8% and 3%), increased appetite (5% and 1%), and weight increased (5% and 1%). Table 20 summarizes the most common adverse events in the pooled dataset.

Table 20: Adverse Reactions Occurring in ≥ 2% of TEV-50717-Treated Patients and More Frequently than in Placebo-Treated Patients, Studies 30046 and 30060

MedDRA Preferred Term	Total placebo (N=110)	% Total Placebo	Total TEV-50717 (N=164)	%Total TEV-50717
Headache*	10	9%	22	13%
Somnolence*	2	2%	18	11%
Fatigue	3	3%	13	8%
Increased appetite	1	1%	8	5%
Weight increased	1	1%	8	5%
Diarrhea	1	1%	6	4%
Irritability	1	1%	6	4%
Insomnia*	2	2%	5	3%
Enuresis	0	0%	4	2%
Gastroenteritis*	1	1%	4	2%
Epistaxis	1	1%	3	2%
Hyperhidrosis	0	0%	3	2%
Restlessness	0	0%	3	2%
Viral infection	0	0%	3	2%

*Grouped Term
Headache – headache, migraine, migraine with aura
Somnolence – somnolence, sedation, hypersomnia
Insomnia - initial insomnia, insomnia, middle insomnia
Gastroenteritis - gastroenteritis, gastroenteritis viral
[Source: Reviewer created from adae.xpt]

Table 21 shows the most frequently reported TEAEs with long-term, open-label treatment in Study 30047. Headache, somnolence, and increased weight were common among patients exposed to deutetrabenazine in Study 30047, as in the short-term placebo-controlled efficacy studies.

Table 21: Most Frequently-Reported Treatment-Emergent Adverse Events, Study 30047

MedDRA preferred term	Total (N=227) n (%)
Patients with any TEAE	**161 (70.9)**
Headache	30 (13.2)
Somnolence	28 (12.3)
Nasopharyngitis	23 (10.1)
Weight increased	22 (9.7)
Anxiety	17 (7.5)
Tic	15 (6.6)
Vomiting	15 (6.6)
Pyrexia	13 (5.7)
Fatigue	11 (4.8)
Upper respiratory tract infection	11 (4.8)
Influenza	10 (4.4)
Nausea	10 (4.4)
Diarrhea	9 (4.0)

[Source: Adapted from Applicant's Summary of Clinical Safety, Table 30, page 81]

In the randomized withdrawal portion of Study 30047, 84 patients were randomized to TEV-50717 and 42 patients were randomized to placebo. The most common adverse events in the TEV-5017 group that occurred more frequently than in the placebo group were insomnia and pyrexia, both occurring in two patients (2.4%) in the TEV-50717 group and zero patients in the placebo group.

The adverse events that occurred in more than one patient in C-17 (open-label pilot study) included fatigue, headache, irritability, nasopharyngitis, diarrhea, somnolence, and hyperhidrosis.

As described in the prescribing information, common adverse reactions reported with deutetrabenazine clinical trials in patients with HD were somnolence, diarrhea, dry mouth, fatigue, urinary tract infection, insomnia, anxiety, constipation, and contusion. In the TD studies, the most common adverse reactions were nasopharyngitis, insomnia, depression/dysthymic disorder, and akathisia/agitation/restlessness.

Of note, the populations for which deutetrabenazine is currently indicated differed from the TS population in terms of age, co-occurring disorders, and concomitant medications. However, the adverse event profile in the pediatric TS population overlaps with that of the adult HD population, with somnolence, fatigue, and diarrhea reported in ≥ 4% of deutetrabenazine-

treated patients in both populations. Insomnia was reported in ≥ 4% of deutetrabenazine-treated patients in all three development programs.

A notable difference in the pediatric TS development program was that increased appetite and increased weight were reported frequently as adverse events; these adverse events were not commonly reported in the studies (b) (4) Patients exposed to deutetrabenazine in the TS studies also reported irritability more frequently than patients in the placebo group (4% versus 1%). Although reported in the studies for the adult indications, dry mouth, urinary tract infection, constipation, and contusion were not frequently reported adverse events in the TS development program. Anxiety, more common in deutetrabenazine-treated patients than in patients on placebo in the HD program, was reported in the same proportion (3%) of deutetrabenazine-treated and placebo-treated patients in the TS studies. Anxiety was commonly reported among patients receiving open-label treatment with deutetrabenazine in the open-label study 30047 (8% of patients).

Depression and Suicidal Ideation and Behavior

The Prescribing Information for deutetrabenazine includes a boxed warning regarding the risk of depression and suicidal ideation and behavior in patients with HD. However, in the pediatric TS development program, a greater proportion of patients on placebo reported depression as an adverse event (2% of patients in the deutetrabenazine treatment groups and 3% of patients in the placebo groups). A greater proportion of placebo-treated patients also reported suicidal ideation or behavior as an adverse event (1% of deutetrabenazine-treated patients compared with 4% of placebo-treated patients). In Study 30047, eight patients (3%) reported depression (depressed mood, depression, feeling of despair), one patient experienced an SAE of self-injurious ideation, and one patient reported an SAE of suicidal ideation. In Study C-17 one patient reported suicidal ideation and one patient reported depression as an adverse event during the treatment period. Another patient reported an adverse event of depression during the 30-day safety follow-up period. (Please see Section 8.2.6 for additional details on regarding assessment of depression using the Children's Depression Inventory (CDI-2) and the C-SSRS.)

Agitation, Restlessness, and Akathisia

Deutetrabenazine carries a warning regarding the risks of agitation, restlessness, and akathisia. In the double-blind, placebo-controlled studies in patients with HD, these symptoms were reported by 4% of patients (compared to 2% of patients on placebo). In the TD development program, these symptoms were reported by 2% of patients (compared to 1% of patients on placebo). Agitation (including preferred terms of agitation, anger, aggression) was reported in two patients (4%) in the high-dose treatment arm of Study 30060 (and no patients in the low-dose arm or the placebo group). In the TS development program overall, agitation was reported by 2% of placebo-treated patients and 1% of deutetrabenazine-treated patients in the controlled studies. Restlessness was reported in 2% of patients exposed to deutetrabenazine (and no patients in the placebo group) and akathisia was reported in a total of one placebo-treated patient and one deutetrabenazine-treated patient in Studies 30046 and 30060. In Study

30047, one patient reported restlessness and five patients (2%) reported agitation. No patients reported akathisia in Study 30047. One patient in Study C-17 reported restlessness during the 30-day follow-up period after medication discontinuation.

Parkinson-like Events

Deutetrabenazine carries a warning regarding the risk of parkinsonism. The Applicant used a Standardized MedDRA query (SMQ) to identify patients who experienced Parkinson-like adverse events. Two patients who received deutetrabenazine in Study 30046 experienced an adverse event of tremor; no patients in the placebo group reported any Parkinson-like adverse events. The tremors resolved without a change in study medication. No Parkinson-like adverse events were reported in Study 30060. In open-label Study 30047, two additional patients reported adverse events of tremor and one patient reported an adverse event of bradyphrenia. These events also resolved without a change study medication. In Study C-17, one patient reported an adverse event of dyskinesia. No action was taken with the study medication and the patient recovered.

Hyperprolactinemia and Related Adverse Events

The prescribing information for deutetrabenazine includes a warning regarding the risk of hyperprolactinemia because tetrabenazine, a closely related VMAT2 inhibitor, elevates serum prolactin concentrations in humans. Serum prolactin levels were not collected in the clinical trials that evaluated deutetrabenazine in the TD and HD populations. Serum prolactin levels were also not included in the routine laboratory assessments in the TS development program. One patient (Patient (b) (6)) reported adverse events of hyperprolactinemia, breast enlargement, and breast tenderness during open-label treatment in Study 30047. One patient in the placebo group reported irregular menses; there were no reports of irregular menses in patients treated with deutetrabenazine. No patients reported galactorrhea in the TS development program.

Clinical Reviewer Comment: *Several of the most commonly reported adverse events in the HD and TD development programs were also reported frequently in the pediatric TS program–namely somnolence, fatigue, and insomnia. The most notable difference in the pattern of adverse events seen in the pediatric TS development program compared with the HD and TD programs was the frequency with which increased appetite and increased weight were reported. This risk will be noted in Section 8.4 of the prescribing information. In contrast with the HD and TD programs, depression, suicidal ideation and behavior, agitation, akathisia, and restlessness did not appear to be more common among patients receiving deutetrabenazine as compared with placebo. Parkinsonism and Parkinson-like events are a known risk of deutetrabenazine in the HD and TD populations; more patients receiving deutetrabenazine reported Parkinson-like events than patients receiving placebo, though the total number of patients reporting these symptoms was small and the symptoms resolved spontaneously. Hyperprolactinemia is a potential risk with deutetrabenazine given that it has occurred tetrabenazine, a closely related VMAT inhibitor. Serum prolactin was not systematically*

assessed in the TS program, but spontaneous reports of hyperprolactinemia and related events were rare.

Laboratory Findings

The serum chemistry panel in Studies 30046 and 30060 included electrolytes, divalents, liver transaminases, bilirubin, cholesterol, albumin, protein, lactate dehydrogenase, and urate. The hematology assessments included hemoglobin, hematocrit, red blood cell count, mean platelet volume, platelet count, and white blood cell count and differential. Laboratory assessments were performed at baseline and at the end of treatment (Week 12 in Study 30046 and Week 8 in Study 30060).

Baseline mean values for collected laboratory assessments were comparable in all treatment groups. Mean changes from baseline over the course of the study were small in all treatment groups. Table 22 and Table 23 show the mean changes from baseline for selected laboratory assessments in Studies 30046 and 30047.

Table 22: Mean Change from Baseline to Week 12, Selected Laboratory Parameters, Study 30046

Laboratory Parameter	Mean Change from Baseline (Standard Deviation)	
	Placebo (N=59)	TEV-50717 (N=58)
ALT (U/L)	-0.9 (6.3)	1.9 (8.2)
AST (U/L)	-0.6 (3.7)	0.4 (5)
Total Bilirubin (µmol/L)	-0.1 (3.5)	-0.3 (4.6)
Direct Bilirubin (µmol/L)	0 (1)	-0.1 (1.4)
Creatinine (µmol/L)	1.7 (5)	2 (7.8)
Glucose (mmol/L)	0.1 (0.9)	-0.2 (1)
Cholesterol (mmol/L)	0.1 (0.6)	0.03 (0.5)
Hemoglobin (g/L)	0.5 (6.8)	0.9 (5.7)
Hematocrit %	0.004 (0.02)	0.004 (0.02)
Leukocytes (GI/L)	-0.3 (2)	-0.4 (1.6)
Neutrophils (GI/L)	-0.1 (1.5)	-0.1 (1.3)
Platelets (GI/L)	4.2 (45.7)	-11.2 (45.5)

ALT=alanine aminotransferase; AST=aspartate aminotransferase
[Source: Adapted from Clinical Study Report, 30046, Tables 14.3.4.1.1 and 14.3.4.2.1]

Table 23: Mean Change from Baseline to Week 8, Selected Laboratory Parameters, Study 30060

Laboratory Parameter	Mean Change from Baseline (Standard Deviation)		
	Placebo N=51	Low-Dose TEV-50717 N=54	High-Dose TEV-50717 N=52
ALT (U/L)	-2.1 (7.1)	0.5 (9)	1.5 (9.3)
AST (U/L)	-1.4 (5.2)	0.2 (5)	0.4 (5.6)
Bilirubin (µmol/L)	0.7 (4.9)	-0.1 (3.3)	0.6 (2.8)
Direct Bilirubin (µmol/L)	0 (1.3)	-0.2 (1.3)	-0.2 (1)
Creatinine (µmol/L)	0.5 (5)	-0.3 (7)	5.8 (20)
Glucose (mmol/L)	-0.27 (0.6)	0 (0.8)	0.1 (0.7)
Cholesterol (mmol/L)	-0.1 (0.6)	-0.03 (0.6)	0.2 (0.5)
Hemoglobin (g/L)	0.1 (6.8)	-0.4 (5.6)	0 (7.4)
Hematocrit %	-0.001 (0.02)	0 (0.02)	0.003 (0.02)
Leukocytes (GI/L)	-0.07 (1.6)	-0.11 (1.6)	-0.36 (2.2)
Neutrophils (GI/L)	-0.2 (1.5)	0.005 (1.3)	-0.6 (2)
Platelets (GI/L)	-11 (32)	2.9 (39)	-2.1 (42)

[Source: Adapted from Clinical Study Report, 30060, Tables 14.3.4.1.1 and 14.3.4.2.1]

I reviewed the line listings for all chemistry and hematology values that fell outside of the reference range. The deviations from the reference range were generally small and unlikely to

be clinically meaningful. The Applicant analyzed shifts from baseline to the end of treatment for laboratory assessments. Table 24 shows shifts from the normal range to higher than the normal range for selected chemistry assessments in Studies 30046 and 30060.

Although a higher proportion of patients in the TEV-50717 groups shifted from normal to high aspartate aminotransferase (ALT) and total bilirubin values than in the placebo group, the absolute number of patients experiencing these shifts and the magnitude of the changes were relatively small. In patients treated with deutetrabenazine, the maximum ALT value observed in the studies was 66 U/L (reference range 0 to 47 U/L) and the maximum total bilirubin value was 36 µmol/ L (reference range 0 to 22 µmol/L). No cases of Hy's law/drug-induced liver injury were identified.

Serum creatinine elevations were also more common in patients treated with deutetrabenazine than placebo, though again the absolute numbers and the magnitude of change were small. Shifts in two patients exposed to deutetrabenazine in Study 30060 appeared to be potentially clinically meaningful. Patient (b) (6) is a 10-year-old female whose serum creatinine rose from 42.4 µmol/L to 155.6 µmol/L (age adjusted reference range 37.1 to 69 µmol/L). She also reported an adverse event of dysuria and was discontinued from the study. Serum creatinine increased from 66.3 µmol/ L to 139.7 µmol/ L (reference range 47.7 to 84 µmol/L) in a 15-year-old patient (b) (6) This patient reported adverse events of fatigue and somnolence, which resolved, and the patient completed the study.

No clinically meaningful pattern was otherwise discernible in the proportion of patients shifting from normal range to out of range values in Studies 30046 and 30060.

Table 24: Shifts from Normal Range to Higher than Normal Range, Selected Chemistry Assessments, Studies 30046 and 30060

Laboratory Parameter	Placebo N=110 (n%)	TEV-50717 – All Groups N=164 (n%)
ALT	1 (0.9%)	5 (3%)
AST	0	0
Total Bilirubin	1 (0.9%)	3 (2%)
Direct Bilirubin	1 (0.9%)	1 (0.6%)
Creatinine	1 (0.9%)	6 (4%)
Glucose	4 (4%)	5 (3%)
Cholesterol	13 (12%)	23 (14%)

[Source: Reviewer created]

Few patients in Studies 30046 and 30060 moved from the normal range to below the normal range in chemistry values. Two patients in the TEV-50717 treatment groups and one patient in the placebo groups shifted from normal to below-normal glucose. One patient who received TEV-50717 and one patient who received placebo shifted from normal to below normal creatinine.

There were few shifts from normal to outside of the normal range in hematology values in Studies 30046 and 30060.

In Study 30047, laboratory assessments were collected on Weeks 8, 28, and 54. A review of the laboratory data from this uncontrolled study did not identify any clinically meaningful trends in any laboratory parameter or any unexpected safety signals.

Clinical Reviewer Comment: *Laboratory assessments were comparable at baseline and at the end-of-treatment in patients exposed to deutetrabenazine compared to placebo. Although the proportion of patients shifting from normal to out-of-range values was numerically higher in the deutetrabenazine treatment groups, the number of patients with potentially clinically meaningful changes was small. Overall, no clinically meaningful trends in laboratory assessments were apparent in data from short-term controlled studies or the long-term, open-label extension.*

Vital Signs

Vital signs were measured at screening, baseline, and Weeks 2, 4, ,6, 9, 12, and 13 in Study 30046. Vital signs were measured at screening, baseline, and Weeks 2, 4, 8, and 9 in Study 30060. The following vital signs and growth parameters were collected in Studies 30046, 30060, and 30047: heart rate (supine/seated and standing), systolic blood pressure (supine/seated and standing), diastolic blood pressure (supine/seated and standing), temperature, and respiratory rate.

Table 25 lists the Applicant's definitions of potentially clinically significant vital sign abnormalities, based on age.

Table 25: Criteria for Potentially Clinically Meaningful Vital Sign Changes, Studies 30046 and 30060

Parameter (unit)	Age (years)	Markedly Low	Markedly High
Systolic blood pressure (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
Diastolic blood pressure (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

[Source: Clinical Study Report, 30046, Table 4, page 67]

Table 26 and Table 27 summarize the proportion of patients with out-of-range post-baseline vital signs values in Studies 30046 and 30060, respectively. Out-of-range values were uncommon in all treatment groups and no clear pattern of effect on vital sign parameters was observed.

Table 26: Abnormal Post-baseline Vital Sign Assessments, Study 30046

Parameter (unit)	Number (%) of Patients		
	TEV-50717 (N=58)	Placebo (N=59)	Total (N=117)
Supine or seated systolic blood pressure (mmHg)			
Abnormally low	0	1 (1.7)	1 (0.9)
Abnormally high	2 (3.4)	1 (1.7)	3 (2.6)
Standing systolic blood pressure (mmHg)			
Abnormally low	1 (1.7)	1 (1.7)	2 (1.7)
Abnormally high	3 (5.2)	2 (3.4)	5 (4.3)
Supine or seated diastolic blood pressure (mmHg)			
Abnormally low	1 (1.7)	0	1 (0.9)
Abnormally high	4 (6.9)	1 (1.7)	5 (4.3)
Standing diastolic blood pressure (mmHg)			
Abnormally low	0	0	0
Abnormally high	0	0	0
Supine or seated pulse rate (bpm)			
Abnormally low	0	1 (1.7)	1 (0.9)
Abnormally high	0	0	0
Standing pulse rate (bpm)			
Abnormally low	0	0	0
Abnormally high	1 (1.7)	0	1 (0.9)

bpm=beats per minute
[Source: Clinical Study Report, 30046, Table 30, page 130]

Table 27: Abnormal Post-baseline Vital Sign Assessments, Study 30060

Vital signs variable, unit	n/M (%) of patients			
	TEV-50717 high dose (N=52)	TEV-50717 low dose (N=54)	Placebo (N=51)	Total (N=157)
Supine or seated systolic blood pressure (mmHg)				
Abnormally low	1/50 (2.0)	0/54	0/51	1/155 (0.6)
Abnormally high	1/50 (2.0)	0/54	3/51 (5.9)	4/155 (2.6)
Standing systolic blood pressure (mmHg)				
Abnormally low	1/49 (2.0)	0/54	0/51	1/154 (0.6)
Abnormally high	0/49	1/54 (1.9)	4/51 (7.8)	5/154 (3.2)
Supine or seated diastolic blood pressure (mmHg)				
Abnormally low	1/50 (2.0)	0/54	0/51	1/155 (0.6)
Abnormally high	3/50 (6.0)	2/54 (3.7)	2/51 (3.9)	7/155 (4.5)
Standing diastolic blood pressure (mmHg)				
Abnormally low	1/49 (2.0)	0/54	0/51	1/154 (0.6)
Abnormally high	2/49 (4.1)	1/54 (1.9)	1/51 (2.0)	4/154 (2.6)
Supine or seated pulse rate (bpm)				
Abnormally low	3/50 (6.0)	2/54 (3.7)	0/51	5/155 (3.2)
Abnormally high	1/50 (2.0)	0/54	0/51	1/155 (0.6)
Standing pulse rate (bpm)				
Abnormally low	1/49 (2.0)	0/54	0/51	1/154 (0.6)
Abnormally high	0/49	0/54	0/51	0/154

bpm=beats per minute
[Source: Clinical Study Report, 30060, Table 25, page 129]

Patients who were exposed to TEV-50717 in Study 30046 were more likely to report orthostatic hypotension and tachycardia than patients in the placebo group (**Table 28**). One patient reported an adverse event of postural orthostatic tachycardia syndrome.

Table 28: Orthostatic Heart Rate and Blood Pressure Changes, Study 30046

Vital Sign Parameter	Placebo N=59	TEV-50717 N=58
Orthostatic tachycardia	6/59 (10%)	13/58 (22%)
Orthostatic SBP	1/59 (2%)	3/58 (5%)
Orthostatic DBP	3/59 (5%)	5/58 (9%)

SBP – systolic blood pressure; DBP – diastolic blood pressure
[Source: Reviewer created from advs.xpt]

For other vital signs assessments, the mean changes from baseline to the end of treatment

were small and unlikely to be clinically meaningful; no clinically meaningful difference between the TEV-50717 groups and placebo groups was apparent. In Study 30060, the frequency of orthostasis in the high-dose group was greater than in the placebo group, but differences between the low-dose group and the placebo group were less clear (Table 29). These data raise the possibility that orthostatic changes could be dose related.

Table 29: Orthostatic Heart Rate and Blood Pressure Changes, Study 30060

Vital Sign Parameter	Placebo	Low-Dose TEV-50717 N=54	High-Dose TEV-50717 N=52
Orthostatic tachycardia	4/51 (8%)	7/54 (13%)	7/52 (13%)
Orthostatic SBP	1/51 (2%)	0	0
Orthostatic DBP	4/51 (8%)	3/54 (6%)	6/52 (12%)

SBP – systolic blood pressure; DBP – diastolic blood pressure
[Source: Reviewer created from advs.xpt]

In the open-label extension (Study 30047), 14/227 patients (6%) and 13/227 patients (6%) experienced abnormally high diastolic blood pressure (seated/supine) and systolic blood pressure (supine/seated). However, most elevations were not sustained and values returned to the normal range. 26/227 (11%) experienced orthostatic hypotension during the study. No patients reported adverse events related to orthostasis.

Clinical Reviewer Comment: *Patients exposed to deutetrabenazine had higher rates of orthostatic vital sign changes, though differences between deutetrabenazine and placebo were less apparent in the fixed-dose study (Study 30060). No other clearly clinically meaningful trends in vital signs was observed in the studies.*

Weight

Increased weight was reported as an adverse event in 5% of patients treated with deutetrabenazine in Studies 30046 and 30060, compared with 1% of patients on placebo. The mean change from baseline at the end of treatment in Study 30046 was 3.23 kg in the TEV-50717 treatment arm and 0.84 kg in the placebo group (Table 30). In Study 30060, the mean change in weight from baseline in the TEV-50717 high-dose and low-dose groups was 2 kg and 2.6 kg, respectively, compared with 0.34 kg on placebo (Table 31).

Table 30: Mean Change in Weight from Baseline to End of Treatment, Study 30046

	Number (%) of Patients		
Visit Parameter	**TEV-50717 (N=58)**	**Placebo (N=59)**	**Total (N=117)**
Baseline (kg)			
n	57	58	115
Mean (SD)	50.91 (22.011)	53.47 (24.385)	52.20 (23.172)
Median	45.00	49.50	48.00
Minimum, maximum	23.0, 109.0	22.0, 128.0	22.0, 128.0
Week 12 (kg)			
n	50	55	105
Mean (SD)	54.87 (22.919)	55.33 (24.747)	55.11 (23.781)
Median	50.30	51.60	51.00
Minimum, maximum	24.0, 116.6	22.2, 133.1	22.2, 133.1
Change from baseline at week 12 (kg)			
n	50	55	105
Mean (SE)	3.23 (0.385)	0.84 (0.329)	1.98 (0.276)
Median	2.35	1.00	1.70
Minimum, maximum	-2.6, 11.8	-6.2, 6.5	-6.2, 11.8

SD=standard deviation; SE: standard error.
Note: Baseline was defined as the last measurement on or prior to the first dose of study drug on day 1. Two patients had incorrect baseline weights in the database. The post hoc analysis of baseline weight presented here excluded these 2 patients.
[Source: Clinical Study Report, 30046, Table 34, page 135]

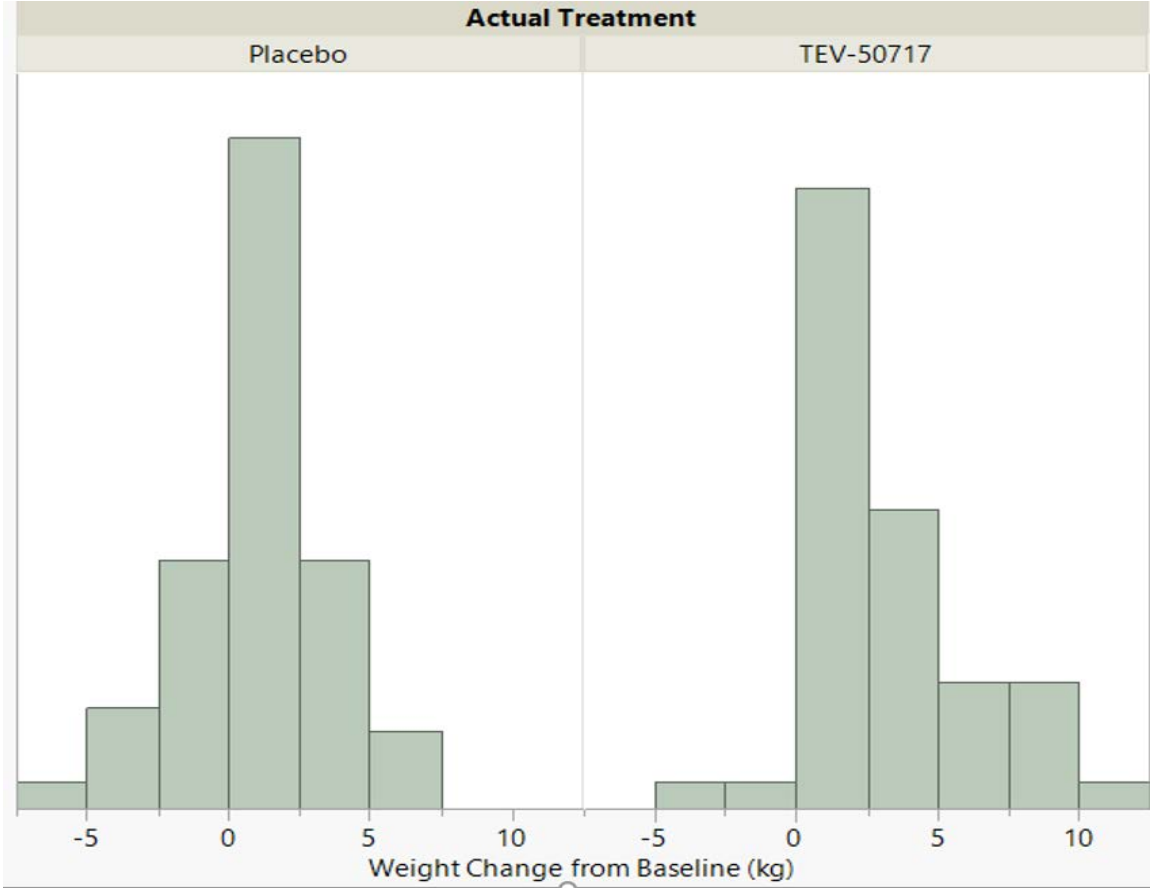
Table 31: Mean Change in Weight from Baseline to End of Treatment, Study 30060

Visit Parameter	Number (%) of patients			
	TEV-50717 high-dose (N=52)	TEV-50717 low-dose (N=54)	Placebo (N=51)	Total (N=157)
Baseline (kg)				
n	52	54	51	157
Mean	47.92	53.94	49.76	50.59
SD	17.393	22.918	17.014	19.406
SE	2.412	3.119	2.382	1.549
Median	45.00	50.00	48.00	48.00
Min, max	25.0, 101.0	20.0, 132.0	24.0, 98.0	20.0, 132.0
Week 8 (kg)				
n	48	51	49	148
Mean	50.68	55.36	50.91	52.37
SD	17.463	20.678	17.045	18.508
SE	2.521	2.895	2.435	1.521
Median	49.45	53.80	49.00	50.45
Min, max	27.0, 101.5	20.7, 105.0	24.3, 103.0	20.7, 105.0
Change from baseline at week 8 (kg)				
n	48	50	49	147
Mean	1.99	2.55	0.34	1.63
SD	1.880	3.028	1.773	2.478
SE	0.271	0.428	0.253	0.204
Median	1.45	2.00	0.40	1.00
Min, max	-1.0, 7.9	-3.2, 17.0	-5.5, 5.0	-5.5, 17.0

SD=standard deviation; SE: standard error.
[Source: Clinical Study Report, 30060, Table 26, page 132]

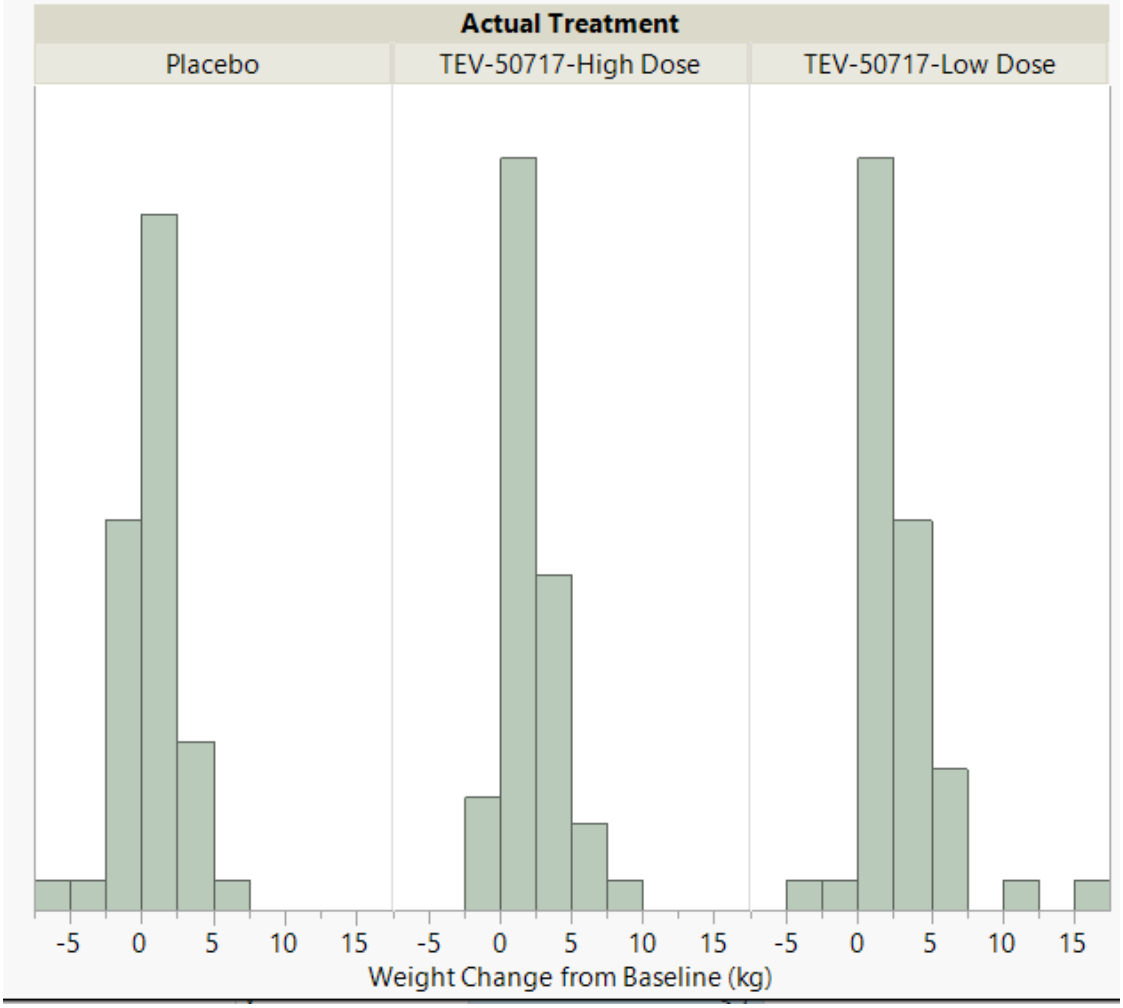
Patients treated with deutetrabenazine in the controlled studies were more likely to experience marked changes in weight over the course of the study. In Study 30046, 11/50 (22%) patients with Week 12 weight assessments in the TEV-50717 treatment arm experienced ≥ 5kg weight gain by the end of treatment, compared with 3/55 (5%) patients in the placebo arm (Figure 4). In Study 30060, 4/47 patients in the high-dose TEV-50717 arm, 7/51 patients in the low-dose TEV-50717 arm, and 1/48 patients in the placebo arm with Week 8 weight assessments experienced ≥ 5kg weight gain by the end of treatment (Figure 5).

Figure 4: Weight Change from Baseline to Week 12 (End of Treatment), Study 30046



[Source: advs.xpt]

Figure 5: Weight Change from Baseline to Week 8 (End of Treatment), Study 30060



[Source: advs.xpt]

Table 32 summarizes the Applicant's analysis of shifts from baseline in age and sex-adjusted BMI categories (underweight, normal, overweight, obese) in Studies 30046 and 30060. Patients exposed to TEV-50717 were more likely to move from the normal weight category to the overweight category over the course of the studies.

Table 32: Shifts from Baseline in Age and Sex-Adjusted BMI Categories, Pooled Analysis Set, Studies 30046 and 30060

Category	Baseline																			
	Pooled Placebo (N=110)				TEV-50717 (N=58)				TEV-50717 High Dose (N=52)				TEV-50717 Low Dose (N=54)				Pooled TEV-50717 (N=164)			
	UW	Nor	OW	Ob	UW	Nor	OW	Ob	UW	Nor	OW	Ob	UW	Nor	OW	Ob	UW	Nor	OW	Ob
Week 8																				
UW	0	0	0	0					2 (4.2)	0	0	0	3 (5.9)	0	0	0	5 (5.1)	0	0	0
Nor	0	28 (58.3)	0	0					1 (2.1)	21 (43.8)	0	0	2 (3.9)	15 (29.4)	0	0	3 (3.0)	36 (36.4)	0	0
OW	0	2 (4.2)	6 (12.5)	3 (6.3)					0	8 (16.7)	5 (10.4)	0	0	6 (11.8)	4 (7.8)	0	0	14 (14.1)	9 (9.1)	0
Ob	0	0	0	9 (18.8)					0	1 (2.1)	1 (2.1)	9 (18.8)	0	1 (2.0)	2 (3.9)	18 (35.3)	0	2 (2.0)	3 (3.0)	27 (27.3)
Missing	3	32	6	20					2	2	0	0	0	0	0	3	4	31	9	20
Week 12																				
UW	2 (3.8)	0	0	0	0	0	0	0									0	0	0	0
Nor	0	24 (46.2)	1 (1.9)	0	2 (4.0)	21 (42.0)	0	0									2 (4.0)	21 (42.0)	0	0
OW	0	2 (3.8)	3 (5.8)	0	0	4 (8.0)	2 (4.0)	0									0	4 (8.0)	2 (4.0)	0
Ob	0	0	1 (1.9)	19 (36.5)	0	1 (2.0)	5 (10.0)	15 (30.0)									0	1 (2.0)	5 (10.0)	15 (30.0)
Missing	1	36	7	13	0	3	2	2									10	57	14	32

BMI=body mass index; Nor=Normal; Ob=obese; OW=overweight; UW=underweight.
TEV-50717=patients exposed to TEV-50717 in Study 30046
TEV-50717 high-dose=patients exposed to high-dose TEV-50717 in Study 30060
TEV-50717 low-dose=patients exposed to low-dose TEV-50717 in Study 30060
Note: Percentages were based on the number of patients who had values at both baseline and week 8/12. Baseline was defined as the last measurement on or prior to the first dose of study drug. Age and sex-based BMI categories included: underweight (<5 percentile), normal (≥5 to <85 percentile), overweight (≥85 to <95 percentile), obese (≥95 percentile).
[Source: Applicant's Clinical Summary of Safety, Table 56, page 138]

Increased weight was reported as an adverse event in 22/227 (10%) of patients in the long-term open-label extension study (30047). In Study 30047, the mean change in weight from baseline was 1.5 kg at Week 8 and 4.6 kg at Week 28. The mean change in BMI from baseline was 0.4 kg/m^2 at Week 8 and 1.1 kg/m^2 at Week 28. The mean change in BMI z-score from baseline to Week 28 was 0.22.

Clinical Reviewer Comment: *Patients exposed to deutetrabenazine in the controlled studies were more likely to report increased weight as an adverse event, gained more weight on average over the course of treatment, and were more likely to move into the overweight BMI category than patients on placebo. Mean weight and BMI increased in long-term, open-label treatment. Although increases in weight and BMI are expected in pediatric patients, the data from Study 30047 suggest that weight and BMI may have increased more than expected over the course of 28 weeks, though no control group was included in the long-term study for comparison. Increased weight will be listed as a common adverse reaction in pediatric patients with TS in Section 8.4 of the Prescribing Information.*

Electrocardiograms (ECGs)

Electrocardiograms (ECG) were obtained at screening, baseline, and on Weeks 4, 6, and 12 in Study 30046. ECGs were obtained at screening, baseline, and on Weeks 4 and 8 in Study 30060. The Applicant used the definitions listed in Table 33 to identify patients with potentially clinically meaningful ECG changes.

Table 33: Criteria for Abnormal ECG Parameters by Age

ECG parameter (unit)	Age (years)	Abnormally low	Abnormally high
Heart rate (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

[Source: Clinical Study Report, 30060, Table 5, pages 69 and 70]

Table 34: Abnormal ECG Findings, Study 30046

		Number (%) of Patients		
Parameter (unit) Age Group (years)	**Criterion**	**TEV-50717 (N=58) n/M (%)**	**Placebo (N=59) n/M (%)**	**Total (N=117) n/M (%)**
Mean heart rate (beats/min)				
	Abnormally low	6/58 (10.3)	5/59 (8.5)	11/117 (9.4)
	Abnormally high	0/58	1/59 (1.7)	1/117 (0.9)
PR interval (msec)				
	Abnormally high	3/58 (5.2)	1/59 (1.7)	4/117 (3.4)
QRS duration (msec)				
	Abnormally high	5/58 (8.6)	2/59 (3.4)	7/117 (6.0)

[Source: Adapted from Clinical Study Report, 30046, Table 33, page 133]

Table 35: Abnormal Post-baseline ECG Findings, Study 30060

Parameter (unit) Age group (years)	Criterion	TEV-50717 high dose (N=52) n/M (%)	TEV-50717 low dose (N=54) n/M (%)	Placebo (N=51) n/M (%)	Total (N=157) n/M (%)
Mean heart rate (beats/min)					
Any age	Abnormally low	1/49 (2.0)	2/54 (3.7)	1/51 (2.0)	4/154 (2.6)
Any age	Abnormally high	1/49 (2.0)	0/54	0/51	1/154 (0.6)
PR interval (msec)					
Any age	Abnormally high	3/49 (6.1)	2/54 (3.7)	2/51 (3.9)	7/154 (4.5)
QRS duration (msec)					
Any age	Abnormally high	0/49	0/54	2/51 (3.9)	2/154 (1.3)

[Source: Adapted from Clinical Study Report, 30060, Table 30, page 137]

Clinical Reviewer Comment: *The number of patients experiencing potentially clinically meaningful changes in ECG parameters was generally similar in the TEV-50717 and placebo groups.*

QT

The prescribing information for deutetrabenazine indicates that clinically relevant QT prolongation may occur in patients treated with deutetrabenazine who are CYP2D6 poor metabolizers or who are administered strong CYP2D6 inhibitors. No patients in Studies 30046 or 30047 experienced QTcF interval prolongation ≥ 60 msec from baseline. Two patients in placebo group and one patient on high dose TEV-50717 had a post-baseline QTcF measurement ≥ 440 msec (all < 500 msec). Three patients in Study 30047 had post-baseline QTcF measurements ≥ 440 msec; no patients had a post-baseline QTcF ≥ 450 msec. One patient in Study 30047 had a one-time increase ≥ 60 msec from baseline. As noted previously, doses in the clinical trials were based on CYP2D6 impairment status. No patients in Study C-17 experienced a QT interval prolongation.

Clinical Reviewer Comment: *QT-interval prolongations that were likely to be clinically relevant were not observed in the TS development program.*

Immunogenicity

One patient exposed to low-dose TEV-50717 in Study 30060 reported a hypersensitivity reaction. The other immune system disorders that were reported (allergy to animal and seasonal allergy) were unlikely to be related to study drug exposure.

8.2.5. Analysis of Submission-Specific Safety Issues

Please see the discussion of adverse events related to depression and suicidal ideation and behavior in Sections 8.2.4 and 8.2.6 as well as the discussion of adverse events related to agitation, restlessness, akathisia, and parkinsonism in Section 8.2.4.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) was used to prospectively assess suicidal ideation and behavior in the TS development program. The C-SSRS is a validated risk assessment scale that characterizes the severity of suicidal ideation, ranging from passive suicidal ideation ("wish to be dead") to "active suicidal ideation with specific plan and intent and behaviors." The C-SSRS also asks about the intensity of the suicidal thoughts and whether any suicidal behaviors have occurred.

In Study 30046, two patients in the TEV-50717 group and one patient in the placebo group reported suicidal ideation at baseline on the C-SSRS. One patient in the TEV-50717 group and three patients in the placebo group subsequently reported suicidal ideation on post-baseline C-SSRS assessments. No patients reported suicidal behavior during the study.

In Study 30060, no patients in the TEV-50717 treatment groups and one patient in the placebo group reported suicidal ideation at baseline. One patient each in the low-dose and high-dose TEV-50717 treatment groups and two patients in the placebo group reported suicidal ideation on post-baseline C-SSRS assessments. No patients reported suicidal behavior during the study.

In Study 30047, four patients reported suicidal ideation on the C-SSRS. Suicidal ideation was detected on the C-SSRS for one patient in Study C-17. Suicidal behavior was not reported in these open-label studies.

Clinical Reviewer Comment: *Suicidal ideation and behavior as reported on the C-SSRS were uncommon in the TS development program. The data from the controlled studies were not suggestive of a greater risk of suicidal ideation or behavior in patients who were exposed to deutetrabenazine.*

Children's Depression Inventory (CDI-2)

The Self-Report and Parent versions of the Children's Depression Inventory (CDI-2) were used to prospectively assess depressive symptoms in the TS development program. The CDI-2 has been validated for the assessment of depressive symptoms in patients ages 7 to 17 years. Patients less than 7 years of age in the TS studies did not complete the Self-Report version, but

their parents/caregivers completed the Parent version. The Self-Report version is a 28-item questionnaire. Each item is rated on a 3-point Likert scale (0, 1, or 2); the maximum score is 56 and higher scores indicate higher levels of depressive symptomatology. The Parent version is a 17-item questionnaire, with each item rated on 4-point Likert scale (0,1, 2, 3) and a maximum score of 51.

Table 36 and Table 37 summarize the change from baseline to end of treatment on the CDI-2 in Studies 30046 and 30060. Patients in the treatment groups in both studies had relatively similar baseline CDI-2 scores. Patients who received deutetrabenazine on average did not report more depressive symptoms at the end of treatment than patients receiving placebo.

Table 36: Children's Depression Inventory, Study 30046

Parameter	Placebo N=59	TEV-50717 N=58
Mean Baseline CDI-2 score (Self-Report)	8.1	9.6
Mean Week 12 score (SR)	7	6.7
Mean CFB (SE)	-1.2 (0.64)	-2.7 (0.75)
Mean Baseline CDI-2 score (Parent Report)	15.2	16.6
Mean Week 12 score (P)	12.5	12.9
Mean CFB (SE)	-2.8 (0.74)	-4.2 (0.93)

CDI-2 – Children's Depression Inventory, Second Edition; SR = Self-Report; P = Parent; CFB = Change from Baseline; SE = standard error
[Source: Adapted from Clinical Study Report, 30046, Tables 14.3.8.1 and 14.3.8.3]

Table 37: Children's Depression Inventory, Study 30060

Parameter	Placebo N=51	Low-Dose TEV-50717 N=54	High-Dose TEV-50717 N=52
Mean Baseline CDI-2 score (Self-Report)	8.9	10.6	8.9
Mean Week 12 score (SR)	7.1	7.7	8.2
Mean CFB (SE)	-1.2 (0.64)	-2.9 (0.67)	-0.5 (0.87)
Mean Baseline CDI-2 score (Parent Report)	15.3	17.9	15.8
Mean Week 12 score (P)	13.1	13.4	14.2
Mean CFB (SE)	-2 (0.7)	-4.4 (0.95)	-1.6 (0.87)

CDI-2 – Children's Depression Inventory, Second Edition; SR = Self-Report; P = Parent; CFB = Change from Baseline; SE = standard error
[Source: Adapted from Clinical Study Report, 30060, Tables 14.3.8.1 and 14.3.8.3]

Clinical Reviewer Comment: *Although depression has been identified as a risk of deutetrabenazine exposure in patients with HD, pediatric patients in the TS development program who were treated with deutetrabenazine did not report more depressive symptoms on the CDI-2 than patients on placebo.*

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant analyzed adverse events by age group, sex, and race for a pooled sample of patients in Studies 30046, 30060, and 30047. A higher proportion of female patients reported adverse events (67%) than male patients (49%); the proportion of adverse events in other demographic subgroups was otherwise similar. However, the subgroup analyses were not adequately powered to allow meaningful comparisons between groups.

Approximately 60% of patients in the TS development program were enrolled at sites outside of the United States. In response to an Information request, the Applicant provided additional information on the applicability of the clinical trial data to the U.S. population.

Diagnostic criteria and baseline YGTSS-TTS score were similar across regions in Studies 30046 and 30060. U.S. patients had a greater mean time since TS diagnosis (4 years on average) than patients outside of the United States (average 2 years). Co-occurring conditions, including ADHD, OCD, and physical illnesses, were more common in U.S. patients as were concomitant treatments such as anxiolytics, hypnotics, and stimulants. Antiepileptic use was more common at sites outside of the United States.

U.S. patients and patients at sites outside of the United States were similar in the proportion of male and female patients. Fewer Black patients and multiracial patients enrolled at sites outside of the United States; the populations were otherwise similar in terms of race. Weight, height, and BMI were higher on average in U.S. patients.

A higher percentage of U.S. patients exposed to deutetrabenazine (67%) experienced TEAEs than in deutetrabenazine-treated patients outside of the United States (53%). The most notable differences in the frequency of adverse events was in gastrointestinal disorders (25% of U.S. patients compared with 15% of patients outside of the United States) and psychiatric disorders (25% and 17%). Patients in the United States were also more likely to have these conditions at baseline. Suicidal ideation and behaviors were uncommonly reported in both groups.

Clinical Reviewer Comment: *Patients outside of the United States on average had a shorter duration of illness and fewer comorbidities than patients in the United States. Concomitant medication use was also more common in U.S. patients. Although these factors could theoretically impact the severity of illness, the baseline TS severity as measured by the YGTSS-TTS was similar across georgraphic regions. Patients in the United States weighed more on average at baseline, but the submitted studies used weight-based dosing to ensure adequate exposures. The higher rate of adverse events may be explained by higher rates of medical conditions at baseline; the types of adverse events that were reported were otherwise similar between the groups. Overall, it appears unlikely that the differences in the U.S. and ex-U.S. populations meaningfully affected the efficacy results or obscured serious safety signals in the U.S. population.*

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Not applicable.

Pediatrics and Assessment of Effects on Growth

Please see discussion regarding effects on weight in Section 8.2.4.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant queried the global safety database for postmarketing cases in pediatric patients. The most reported adverse reactions were somnolence, dyskinesia, depression, tic, fatigue, diarrhea, dry mouth, drug interaction, dizziness, dystonia, and abnormal behavior. Five serious cases were reported:

- 14-year-old male with HD: agitation, aggression, suicidal behavior
- 11-year-old female with vocal stereotypy: acute dystonic reaction
- 13-year-old female with HD: dystonia, balance worsening, body stiffness, shaking, multiple falls
- 15-year-old male with HD: new neoplasm, dyskinesia
- 15-year-old male with HD: somnolence, emotional distress, depression, suicidal ideation

The Applicant provided a cumulative tabulation of serious and non-serious adverse reactions from all postmarketing data sources in the 120-day safety update. Adverse reactions were reported most often in the following System Organ Classes (SOCs): General Disorders and Administrative Conditions; Nervous System Disorders; Injury, Poisoning, and Procedural Complications (most commonly, off-label use and falls); and Psychiatric Disorders. Adverse reactions frequently reported in the postmarketing period–somnolence, headache, fatigue, insomnia, depression, suicidal ideation, nausea, diarrhea, dyskinesia, tremor–were consistent with the known safety profile of deutetrabenazine.

The Applicant noted that there have been nine postmarketing reports of blindness. As discussed previously, approved labeling for deutetrabenazine describes a potential risk of ophthalmologic toxicity with prolonged use because deutetrabenazine may bind to melanin-containing tissues. In response to an information request, the Applicant clarified that eight of these reports referred to a single patient who reported an adverse event of blindness related to deutetrabenazine. However, no information about the duration of exposure, dose, prior medical history, concomitant medications, or other relevant clinical parameters was included in the reports and no assessment of the relatedness to deutetetrabenazine could be conducted. The other case referred to a 69-year-old female who reported functional blindness because her eye-lids were closed most of the time, likely in the setting of facial dyskinesias.

The Division of Pharmacovigilance (DPV) provided consultative review of the available reports of blindness in the FDA Adverse Event Reporting System (FAERS). Six unique cases related to blindness were identified; however, none of the cases involved complete blindness and the vision changes described by the patients did not appear to have a unifying pattern or consistent time to onset after initiation of deutetrabenazine treatment. The reports generally lacked clinical information related to concomitant medications, co-occurring conditions, and clinical outcome. DPV will continue to monitor the potential risk for ophthalmologic toxicity with prolonged use of deutetrabenazine because there is biological plausibility related to melanin

deposits in tissues with prolonged use but does not recommend any regulatory action with respect to blindness at this time.

Clinical Reviewer Comment: *Overall, data from the postmarketing setting are consistent with the known safety profile of deutetrabenazine. The Applicant identified one postmarketing case of blindness for which no clinical information was available. The other available postmarketing reports did not include any cases of complete blindness and were insufficient to conclude that there is an association between deutetrabenazine and blindness. DPV will continue to monitor postmarketing data for cases of ophthalmologic toxicity.*

Expectations on Safety in the Postmarket Setting

(b) (4)

8.2.11. Integrated Assessment of Safety

The short-term, controlled efficacy and safety studies and long-term, open-label study submitted by the Applicant were sufficient to allow for analysis of the safety of deutetrabenazine in pediatric patients with TS. The most common adverse events were headache, somnolence, fatigue, increased appetite, and increased weight. Patients on deutetrabenazine gained more weight than patients on placebo in the controlled studies. QT prolongation, depression, suicidal ideation, and parkinsonism have been identified as safety risks in other indications for which deutetrabenazine is approved. However, these risks were not observed in the pediatric TS development program.

8.3. Statistical Issues

No statistical issues were identified during the review of the studies.

8.4. Conclusions and Recommendations

Deutetrabenazine did not demonstrate either a statistically significant or clinically meaningful treatment effect on tics associated with pediatric TS as measured by the YGTSS-TTS. Safety information obtained in the TS development program will be added to the prescribing information in Section 8.4. No other labeling changes are indicated.

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Pediatrics

Section 8.4 of the Prescribing Information (Pediatric Use) will be updated based on the results of the TS development program. Section 8.4 will indicate that the safety and effectiveness of deutetrabenazine have not been established in pediatric patients for the treatment of TS. Section 8.4 will also list the adverse reactions occurring most commonly in the patients exposed to deutetrabenazine and with a greater incidence in patients on placebo: headache, somnolence, fatigue, increased appetite, and increased weight.

A PWR was issued in January 2020 for studies in pediatric patients ages 6 to 16 years with tics associated with TS. The PWR included a requirement for at least one fixed-dose study, an evaluation of multiple doses with doses based on weight and CY2D6 status, collection of PK data, and an assessment of long-term safety. The Division determined that Studies 30046, 30060, and 30047 fairly responded to the PWR. After review by the Pediatric Exclusivity Board, pediatric exclusivity was granted on May 7, 2021.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Section 8.4 (Pediatric Use) was updated with the results of the TS development program. Efficacy and safety in pediatric patients with TS were not established. (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13 Postmarketing Requirements and Commitment

Not applicable.

14 Appendices

14.1. References

1. American Psychiatric Association, 2013, Diagnostic and Statistical Manual of Mental Disorders (5th ed.).

2. Bitsko RH, JR Holbrook, SN Visser, JW Mink, SH Zinner, RM Ghandour, SJ Blumberg, 2014, A National Profile of Tourette Syndrome, 2011-2012, J Dev Behav Pediatr, 35(5):317–22.

3. Robertson M, V Eapen, HS Singer, D Martino, JM Scharf, P Paschou, V Roessner, DW Woods, M Hariz, CA Mathews, R Crncec, JF Leckman, 2017, Gilles de la Tourette Syndrome, Nat Rev Dis Primers 3, 16097, doi: 10.1038/nrdp.2016.97.

4. Pringsheim T, Y Holler-Managan, MS Okun, J Jankovic, J Piacentini, AE Cavanna, D Martino, K Müller-Vahl, DW Woods, M Robinson, E Jarvie, V Roessner, M Oskoui, 2019, Comprehensive Systematic Review Summary: Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders, Neurology, 92(19):907–915.

5. Pringsheim T, MS Okun, K Muller-Vahl, D Martino, J Jankovic, AE Cavanna, DW Woods, M Robinson, E Jarvie, V Roessner, M Oskoui, Y Holler-Managan, J Piacentini, 2019, Practice Guideline Recommendations Summary: Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders, Neurology, 92:896–906.

6. Osland ST, TDL Steeves, T Pringsheim, 2018, Pharmacological Treatment for Attention Deficit Hyperactivity Disorder (ADHD) in Children with Comorbid Tic Disorders, Cochrane Database of Systematic Reviews, Issue 6.

14.2. Financial Disclosure

The Applicant submitted certification of financial interests and arrangements for clinical investigators involved in the TS clinical studies. The Applicant identified one Investigator, (b) (6) (b) (6) who previously received significant payments from the Applicant for (b) (6) travel/lodging, food, central rater work, and consulting services. (b) (6) The Applicant did not disclose any interests or arrangements which raised questions about the integrity of the study data.

Covered Clinical Study (Name and/or Number): All Covered Clinical Studies Submitted in Support of the Application

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of principal investigators identified: 90		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

Two additional juvenile rat toxicity studies were conducted, one with a major active metabolite of deutrabenazine (d6 β-Dihydrotetrabenazine (SD-949)) and the other with a minor metabolite of deutetrabenazine (SD-1021). Both studies were adequately conducted and no adverse toxicities were observed.

Study Title: d6 β-Dihydrotetrabenazine (SD-949) and SD-809: 46-Day Toxicity Study via Twice Daily (BID) Oral Gavage in Juvenile Rats with Reproductive Evaluation during the Recovery Period

Study no.:	DS-2017-035
Conducting laboratory and location:	(b) (4)
Duration:	9-weeks for main study toxicity animals followed by 4-week recovery period before up to a 9-week reproductive assessment
Duration Units:	Weeks
GLP compliance:	Yes
Drug, lot #, and % purity:	SD-949 (major, active metabolite of SD-809), A02782-011P1, 99.7% SD-809, DT20915011. 99.81%

JAS Specific Toxicity:

- No adverse drug-related findings; NOAEL = 7 mg/kg/day
- Increased startle response at 7 mg/kg/day

Methods

Doses:	SD-949: 0, 2.5, 5, 7 mg/kg/day; 2.5 mg/kg/day for comparator SD-809
Frequency of dosing:	Twice daily
Number/Sex/Group:	(see table below)
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.5% carboxymethylcellulose with 0.1% (w/v) polysorbate 80 in deionized water
Route of administration:	ORAL GAVAGE
Species:	rat
Strain:	CD Sprague-Dawley
Age at start of experiment:	Postnatal day (PND) 25
Period of development studied:	Juvenile to sexual maturation
Comment on Study Design and Conduct:	Dose selection was based on a preliminary juvenile rat study at doses of 5, 15, 20 mg/kg/day (study no DP-2017-022); dose-dependent CNS-related clinical signs of hypoactivity, limpness, hunched posture,

	reduced body weight gains, twitches and difficulty handling were observed.
Parameters and Key Endpoints Evaluated:	Rats were treated with either vehicle, SD-949 (metabolite of SD-809), or SD-809 from PND 25 to PND 70. Standard general toxicity parameters were evaluated in addition to growth and development, neurobehavioral evalutions, and reproductive endpoints.
Dosing Solution Analysis:	Analyzed formulations were within 85% to 115% of nominal concentration

Table 38: Study design DS-2017-035

Group	Treatment	Dose (mg/kg/day)	Dose Volume (mL/kg)	Number of animals					
				General toxicity (treatment & recovery)		Reproductive		TK	
				Males	Females	Males	Females	Males	Females
1	Control Article	0	5	10 + 10	10 + 10	20	20	6	6
2	SD-949	2.5	5	10 + 10	10 + 10	20	20	24	24
3	SD-949	5	5	10 + 10	10 + 10	20	20	24	24
4	SD-949	7	5	10 + 10	10 + 10	20	20	24	24
5	SD-809[+]	2.5	5	10 + 10	10 + 10	20	20	24	24

Animals were treated PND 25 to PND 70. +See TK section below
[Source: Reviewer created from Study DS-2016-035]

Observations and Results

Mortality

There were no drug-related deaths in this study. One low dose female from the reproduction phase of the study was euthanized on gestation day (GD) 5 with no overt signs of morbidity. There were no macroscopic findings recorded at necropsy. A normal pregnancy was observed. Microscopic evaluation of reproductive organs showed uterine hemorrhage and inflammation.

Clinical Signs

Isolated, non-dose dependent observations of hair loss, salivation, and skin findings were noted, but were unlikely to be related to drug administration. Animals were observed twice daily for morbidity and mortality.

Body Weight and Food Consumption

There were no drug-related effects on body weight or food consumption in the main toxicity or reproductive groups. Body weights in the general toxicology group were measured daily predose from PND 25-70 and then every 3 to 4 days during recovery. Reproductive/recovery

males and females were weighed daily PND 25 to PND 70 and then every 3 to 4 days until termination. Individual food consumption was measured twice weekly for all groups.

Ophthalmoscopy
There were no ophthalmologic findings in this study. All toxicity group animals received ophthalmoscopy exams using dilation and indirect ophthalmoscope once predose and once during the last week of dosing.

Hematology
There were no drug-related hematology findings in any group in this study. Blood samples were collected PND 71 and PND 99 from the orbital sinus and an adequate battery of hematology and clinical chemistry was evaluated.

Clinical Chemistry
SD-949 females at ≥ 5 mg/kg/day and SD-809 females had slightly decreased triglyceride levels and 7 mg/kg/day males had decreases in glucose compared to controls. All clinical chemistry findings completely recovered by PND 99 and were considered non-adverse.

Sexual Maturation
SD-949 or SD-809 did not adversely affect sexual maturation, preputial separation, vaginal opening, estrus cycle length and number of cycles. All reproduction phase females were observed starting PND 28 for vaginal opening. All reproduction phase males were observed daily for preputial separation starting on PND 38.

Reproductive Capacity
A decrease in number of estrus cycles was observed for 2.5 mg/kg/day SD-949 and SD-809 (3.15 and 3.10 cycles versus 3.3 for controls, respectively); however, this finding had no effect on mating or fertility. The majority of mating pairs in all groups mated at the first estrus cycle after pairing and there was no effect of drug treatment on mating. The conception and fertility index was 94.7 to 100% for all groups including controls. Small decreases were observed in epididymis count in SD-949 MD and HD and sperm count in the right testis in SD-809 with no resulting change in morphology; given the lack of effects on fertility or mating (as mentioned above), these findings were not adverse or drug-related. There were no drug-related cesarean section findings including sex ratio, number of corpora lutea, implantations, resorptions, or sperm parameters.

CNS/ Neurobehavioral Assessment
Neurobehavioral tests were administered during the in-life portion of the study (PND 66 ± 2) to main phase animals and during the recovery phase (PND 87 ± 2) to recovery/reproductive phase animals including locomotor activity, an open field assessment, auditory startle, and learning and memory. There were no drug-related effects on motor activity (horizontal or vertical movements) or on any open field evaluations.

Auditory startle: Males at 7 mg/kg/day had increases in the startle response compared to control (4.9 newtons vs 3.4 newtons) during block 1 on PND 66. This was the only timepoint that had a statistically significant change for males, although all male drug-treated groups had slightly increased startle response compared to controls during all blocks. During the recovery period, females at 7 mg/kg/day had increases in startle response in blocks 2, 3, 4, and 5 compared to controls, as did the SD-809 treated female group during blocks 3 and 4. As statistically significant differences in females were only observed during the recovery period, and not during the treatment period, the toxicological significance of these findings are unclear.

Table 39: Auditory startle in males on PND 66±2

	Vehicle Control	SD-949			SD-809
Dose Group	1	2	3	4	5
Dose (mg/kg/day)		2.5	5	7	2.5

Group /Sex	Occasion PND 66±2	Block 1	Block 2	Block 3	Block 4	Block 5	Habituation (%)
1M	Mean	3.376	2.100	1.994	2.280	2.187	-31.158
	SD	1.4242	0.9486	1.0103	1.0349	1.0666	26.0741
	N	10	10	10	10	10	10
2M	Mean	4.657	2.727	2.801	2.634	2.595	-42.493
	SD	1.1449	0.9936	1.0235	1.1878	1.0569	27.5315
	N	10	10	10	10	10	10
3M	Mean	4.632	2.549	2.433	3.056	2.744	-35.704
	SD	1.4481	0.8992	0.8478	1.1204	1.2164	40.7952
	N	10	10	10	10	10	10
4M	Mean	4.871*	3.213	2.947	2.771	2.666	-42.772
	SD	2.0671	1.8333	1.4074	1.3210	1.5594	25.7237
	M	10	10	10	10	10	10
5M	Mean	3.468	2.332	2.620	2.423	2.270	-36.835
	SD	1.7401	1.4199	1.7107	1.5600	1.4102	18.6368
	M	10	10	10	10	10	10

*p<0.05 Group 1 vs 4.
[Source: Study DS-2017-035]

Table 40: Auditory startle in females on PND 66±2

	Vehicle Control	SD-949			SD-809
Dose Group	1	2	3	4	5
Dose (mg/kg/day)		2.5	5	7	2.5

Group /Sex	Animal Number	Occasion PND 87±2	Block 1	Block 2	Block 3	Block 4	Block 5	Habituation (%)
1F	Mean		2.732	1.614	1.296	1.301	1.272	-48.463
	SD		1.1341	0.8028	0.3999	0.3957	0.4644	16.5336
	N		9	9	9	9	9	9
2F	Mean		3.000	1.487	1.670	1.983	1.562	-43.965
	SD		1.3895	0.7005	1.2200	1.2223	0.8244	32.0783
	N		9	9	9	9	9	9
3F	Mean		3.102	2.295	2.219	2.196	1.932	-36.327
	SD		0.9848	1.5163	1.0090	0.7241	0.6632	13.4782
	N		9	9	9	9	9	9
4F	Mean		3.978	3.297*	3.266**	2.894**	2.569**	-33.248
	SD		1.6402	1.7786	1.6007	1.3432	1.1652	20.6872
	N		10	10	10	10	10	10
5F	Mean		3.777	2.855	2.455†	2.661††	2.082	-40.028
	SD		2.4686	1.5049	1.0151	1.3585	1.0171	16.7742
	N		10	10	10	10	10	10

*p<0.05 Group 1 vs 4, **p<0.01 Group 1 vs 4, †p<0.05 Group 1 vs 5, ††p<0.01 Group 1 vs 5.
[Source: Study DS-2017-035]

Biel water maze: There were no drug-related effects on learning and memory as assessed using the Biel water maze on PND 65 ± 4 and 94 ± 4 (recovery).

Bone Evaluation
There were no drug-related effects in femur length measurements at the terminal and recovery sacrifice timepoints.

Gross Pathology/Organ weights/Histopathology
There were no drug-related macroscopic findings, effects on organ weights, or any histopathological findings in any group at terminal sacrifice or recovery sacrifice. An adequate list of tissues and organs were evaluated.

Toxicokinetics
Blood samples from the jugular vein from toxicokinetic group animals were collected on PND 25 and 70 predose and at time points 0.5, 1, 3, 6, 7, 8, 10, and 24 hours and plasma concentrations of SD-809 and SD-948 (groups 1 and 5 only), and SD-949 (all groups) were measured. Parameters measured included Cmax, Tmax, half-life, and AUC.
Tmax generally occurred at 1 hour in males and females on PND 25, and at 30 minutes in males and females on PND 70. On PND 25, systemic exposure in females as measured by AUC was

similar to males; however, females had slightly higher exposure compared to males at PND 70. Accumulation of SD-949 over the dosing period was observed in females and ranged from 1.15x to 1.36x, while the opposite was seen in males (0.68x, 0.78x, and 0.90x, respectively). Exposure was approximately dose proportional for both sexes.

Table 41: Toxicokinetic parameters for SD-949 from groups 2, 3, and 4

Text Table 6.2-1. Composite TK Parameters of SD-949 in Male and Female Juvenile Rats on PNDs 25 and 70 Following Oral Gavage Administration of SD-949 Twice-Daily for 46 Consecutive Days (Groups 2, 3, and 4)

Sex	Group	Dose (mg/kg/day)	Total Daily Dose (mg.kg/day)	PND	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng•h/mL)	Dose Norm. AUC_{0-t} (ng•h/mL)/(mg/kg/day)	AUC_{0-24} (ng•h/mL)	$t_{1/2}$ (hr)	R_{obs}
F	2	1.25	2.5	25	32.71	7	137.8	55.1	144.2	1.03	NA
	3	2.5	5	25	63.29	1	351	70.2	370.6	1.16	NA
	4	3.5	7	25	78.16	1	415.3	59.3	445.8	1.29	NA
	2	1.25	2.5	70	42.6	0.5	158.8	63.5	166.3	1.00	1.15
	3	2.5	5	70	98.48	0.5	399.8	80.0	424.9	1.15	1.15
	4	3.5	7	70	161.41	0.5	576.2	82.3	606.3	1.08	1.36
M	2	1.25	2.5	25	38.21	7	167.7	67.1	182.8	1.31	NA
	3	2.5	5	25	85.57	7	354.2	70.8	383	1.24	NA
	4	3.5	7	25	88.36	1	454.2	64.9	524.3	1.80	NA
	2	1.25	2.5	70	29.76	0.5	119.6	47.8	125	1.00	0.68
	3	2.5	5	70	72.93	0.5	290.9	58.2	298.8	0.84	0.78
	4	3.5	7	70	93.34	7	426.3	60.9	472.7	1.46	0.9

NA: Not applicable

[Source: Study report DS-2017-035]

Toxicokinetic parameters were also measured on PND 25 and 70 for SD-809, SD-948, and SD-949 after 2.5 mg/kg/day dose of the parent compound SD-809 (Group 5). Tmax varied depending upon compound and was 0.5 hour for SD-809, 1 to 8 hours for SD-948 and 0.5 hour for SD-949 in females only; Tmax was not quantifiable in males for SD-949. For the parent compound SD-809, on PND 25 and 70, systemic exposure as measured by Cmax and AUC was slightly higher in females compared to males. The metabolite SD-948 had PND 25 exposure levels that were comparable between the sexes; however, males had an approximate 13-fold higher exposure when measured on PND 70 compared to females. SD-949 was not measurable in males while females had 2-fold higher exposure levels on PND 25 compared to PND 70.

Table 42: Toxicokinetic parameters for SD-809, SD-948, and SD-949 after administration of 2.5 mg/kg/day SD-809 (Group 5)

Sex	Group	Analyte	Dose (mg/kg/day)	Total Daily Dose (mg.kg/day)	PND	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng•h/mL)	Dose Norm. AUC_{0-t} (ng•h/mL)/(mg/kg/day)	AUC_{0-24} (ng•h/mL)	$t_{1/2}$ (hr)	R_{obs}
F	5	SD-809	1.25	2.5	25	4.21	0.5	4.5	1.8	NC	NC	NA
	5	SD-809	1.25	2.5	70	1.32	0.5	0.3	0.1	NC	NC	NC
M	5	SD-809	1.25	2.5	25	2.93	0.5	3.9	1.6	NC	NC	NA
	5	SD-809	1.25	2.5	70	0.68	0.5	0.2	0.1	NC	NC	NC
F	5	SD-948	1.25	2.5	25	43.74	7	245.9	98.4	286.5	1.86	NA
	5	SD-948	1.25	2.5	70	5.57	1	23.1	9.2	NC	NC	NC
M	5	SD-948	1.25	2.5	25	51.92	8	260.7	104.3	NC	NC	NA
	5	SD-948	1.25	2.5	70	58.55	8	294.9	118	353.4	1.99	NC
F	5	SD-949	1.25	2.5	25	0.63	0.5	0.2	0.1	NC	NC	NA
	5	SD-949	1.25	2.5	70	1.79	0.5	0.4	0.2	NC	NC	NC
M	5	SD-949	1.25	2.5	25	BLQ	NC	NC	NC	NC	NC	NA
	5	SD-949	1.25	2.5	70	BLQ	NC	NC	NC	NC	NC	NC

NA: Not applicable; NC: Not calculable; BLQ: Below the limit of quantitation of 0.50 ng/mL.

[Source: Study report DS-2017-035]

Study Title: SD-1021: 9-Week Toxicity Study via Twice Daily Oral Gavage in Juvenile Rats with Reproductive Evaluation During the Recovery Period

Study no.:	DS-2016-061
Conducting laboratory and location:	(b) (4)
Duration:	9 weeks for main study toxicity animals followed by 4-week recovery period before a 4-week reproductive assessment
Duration Units:	Weeks
GLP compliance:	Yes
Drug, lot #, and % purity:	SD-1021 (metabolite of SD-809), A02877-069P1, 98.8%

JAS Specific Toxicity:

- No adverse drug-related findings; NOAEL = 50 mg/kg/day
- Increased motor activity at 50 mg/kg/day

Methods

Doses:	0, 10, 30, 50 mg/kg/day
Frequency of dosing:	Twice daily
Number/Sex/Group:	(see table below)
Dose volume:	5 mL/kg

Formulation/Vehicle:	0.5% carboxymethylcellulose with 0.1% (w/v) polysorbate 80 in deionized water
Route of administration:	ORAL GAVAGE
Species:	Rat
Strain:	CD Sprague-Dawley Rat
Age at start of experiment:	Postnatal day (PND) 25
Period of development studied:	Juvenile to sexual maturation
Comment on Study Design and Conduct:	This juvenile animal study had a toxicity/recovery, reproductive, and a toxicokinetic portion. Dose selection was based on preliminary PK rat studies showing the above selected doses would bracket the human exposure as well as the FDA Guidance safety testing of drug metabolites
Parameters and Key Endpoints Evaluated:	Rats were treated with vehicle or SD-1021 (metabolite of SD-809) from PND 25 to PND 70. Standard general toxicity endpoints were evaluated in addition to growth and development, neurobehavioral evaluations, and reproductive endpoints.
Dosing Solution Analysis:	Analyzed formulations were within 85% to 115% of nominal concentration

Table 43: Study design DS-2016-061

Group	Treatment	Dose (mg/kg/day)	Dose Volume (mL/kg)	Number of animals					
				General toxicity (treatment & recovery)		Reproductive		TK	
				Males	Females	Males	Females	Males	Females
1	Control Article	0	5	10 + 10	10 + 10	20	20	3	3
2	SD-1021	10	5	10 + 10	10 + 10	20	20	24	24
3	SD-1021	30	5	10 + 10	10 + 10	20	20	24	24
4	SD-1021	50	5	10 + 10	10 + 10	20	20	24	24

[Source: Reviewer created]

Observations and Results

Mortality: None

Clinical Signs

Sporadic hair loss was observed in several high dose males (HDM), and a kinked tail in a single high dose female (HDF), both likely unrelated to drug treatment. There were no other clinical signs in any animal in this study. Animals were observed twice daily for morbidity and mortality.

Body Weight/Food Consumption
There were no drug-related effects on body weight or food consumption. Body weights were measured daily predose from PND 24 to 71 and then twice weekly during the recovery portion until PND 99. Reproductive group males and females were weighed daily PND 25 to PND 80 and then every 3 to 4 days until termination on PND 127 for males or gestation day (GD) 14 or 15 for females. Individual food consumption was measured twice weekly for all groups.

Ophthalmoscopy
There were no ophthalmologic findings. All toxicity group animals had ophthalmoscopy exams using dilation and indirect ophthalmoscope predose and during the last week of dosing.

Hematology/Clinical Chemistry
There were no drug-related hematology or clinical chemistry findings. Blood samples were collected PND 71 and PND 99 and an adequate battery of hematology and clinical chemistry was evaluated.

Sexual Maturation
There were no drug-related findings on sexual maturation including preputial separation, vaginal opening, estrus cycle length, and number of estrous cycles. Reproductive group females were observed daily for vaginal opening starting on PND 28. Reproductive group males were observed daily for preputial separation starting on PND 38.

Reproductive Capacity
The majority of mating pairs in all treatment groups mated at the first estrus cycle after pairing; there was no drug-related effect on mating and there were no differences in estrus cycle activity between the groups. The conception and fertility index was 89% to 100% in all treatment groups; 15, 17, 18, and 20 females successfully mated. Although the number of corpora lutea was statistically significantly decreased at the high dose (HD; 14.8 versus 16.5 for controls), there were no other drug-related cesarean section findings including number of implantations, implantation losses, or resorptions and therefore this finding is likely not treatment related. Additionally, SD-1021 had no effect on estrous cycle activity, mating performance, sperm parameters, or fertility. Prior to first mating, vaginal smears from reproductive group females were taken to determine stage of estrous and continued until evidence of mating was observed or 20 days.

CNS/ Neurobehavioral Assessment
A battery of neurobehavioral tests were administered during the in-life portion of the study to main phase animals (PND 64) and during the recovery phase to recovery/reproductive phase animals (PND 92/93) including locomotor activity, an open field assessment, auditory startle, and learning and memory via the Biel water maze. There were no drug-related effects on any open field evaluations, auditory startle, and on Biel water maze evaluations.

Motor activity: Motor activity was tested using an automated infrared sensor system PND 64 ± 2 and PND 93 ± 2. HDM had significantly increased horizontal and vertical movements

compared to control during the first 5-minute interval and then between minutes 10 and 15. HDF had significantly increased motor activity in the interval minute 15 to 20. These changes were not observed in the recovery period, and these findings did not impair mating or other parameters. There were no other drug-related differences in motor activity.

Bone Evaluation
No drug-related effects on femur length were observed.

Gross Pathology/Organ weights/Histopathology
There were no drug-related macroscopic findings, effects on organ weights, or histopathological findings animals at the end of the dosing period PND 71 or recovery period PND 101, reproductive study males PND 127, or reproductive study females GD 14 or 15. Complete gross pathological examinations were performed on all toxicity and reproductive group animals and an adequate list of tissues and organs were examined for histopathology.

Toxicokinetics
Blood samples from toxicokinetic group animals were collected on PND 25 and 70 predose and at 1, 2, 4, 6, 7, 8, 10, and 24 hours postdose. Tmax for SD-1021 generally occurred at approximately 7 hours postdose on PND 25 and 70. Exposure to SD-1021 as measured by AUC_{0-24} increased as dose increased, albeit at a less than dose proportional amount at some doses, others increased more than dose proportional. There was little to no drug accumulation after repeated dosing of SD-1021 from day 25 to day 70 and there were no apparent sex differences in exposure.

Table 44: Toxicokinetic parameters for SD-1021

Sex	Day	Dose[i] (mg/kg)	Total Daily Dose (mg/kg/day)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng•h/mL)	AUC_{0-24} (ng•h/mL)	$t_{1/2}$ (h)	R_{obs}[ii]
Female	PND 25	5	10	8	134.25	900	900	2.67	NA
		15	30	7	306.19	2318	2318	5.41	NA
		25	50	7	500.05	3960	3960	6.23	NA
	PND 70	5	10	7	183.34	1057	1057	4.04	1.17
		15	30	7	460.84	1977	1977	3.97	0.85
		25	50	7	415.91	3067	3067	3.86	0.77
Male	PND 25	5	10	7	114.83	522	597	1.61	NA
		15	30	7	304.08	2399	2399	4.61	NA
		25	50	7	473.32	3575	3575	3.99	NA
	PND 70	5	10	7	227.00	1082	1082	2.48	1.81
		15	30	7	227.30	1653	1653	3.52	0.69
		25	50	7	484.38	2679	2679	3.57	0.75

[i] Animals received doses of SD-1021 by oral gavage twice-daily (approximately 6 hours [±30 minutes] apart based upon the first animal dosed) on PNDs 25 to 70 at the designated dose levels.
[ii] R_{obs} = $AUC_{0-24,\ PND\ 70}$ divided by $AUC_{0-24,\ PND\ 25}$.
NA: Not applicable.
PND: Postnatal Day; PND 25 = day 1 of dosing; PND 70 = day 46 of dosing.
[Source: Study DS-2016-061]

14.4. Clinical Pharmacology

Bioanalysis: Plasma concentrations of deutetrabenazine and its metabolites, α-HTBZ and β-HTBZ, were quantified using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS; Validation reports: SD-809-CLN-12, DP-2018-028, VR-425-18-01, VR-425-18-02, VR-452-19-01, VR-452-19-01 Addendum, VR-452-19-02, and VR-452-19-02 Addendum). The calibration range for deutetrabenazine is 0.1 ng/mL to 10 ng/mL, for α-HTBZ and β-HTBZ is 0.5 ng/mL to 100 ng/mL. The precision and accuracy values of at least two-thirds of the overall QC samples were within ±15% (±20% at the LLOQ). The analytes in human plasma were stable over 382 days when stored at -80°C. The analytes in human plasma were stable over at least 24 hours at room temperature, at least three freeze-thaw cycles and autosampler stability at 4°C over 197 hours. Up to 10-fold dilution did not affect the precision and accuracy of the measurement of analytes. The validation of the bioanalytical methods appear reasonable.

Population PK analysis: The studies included in the population PK analysis are shown in **Table 45**. A two-compartment PK model with two parallel first-order absorption processes (with different lag times and absorption rate parameters) with linear elimination adequately described the PK of the active metabolites of deutetrabenazine (α-HTBZ and β-HTBZ). A one-compartment PK model with two parallel first-order absorption processes (with different lag

times and absorption rate parameters) with linear elimination adequately described the PK of the parent drug, deutetrabenazine. The combined additive and proportional residual error model on untransformed data adequately explain the PK of parent drug and its active metabolites. Previously developed population PK models for deutetrabenazine and its active metabolites in healthy adult subjects were used for this analysis and the model parameters were re-estimated following inclusion of children and adolescent patients with TS-associated tics. Please refer to the clinical pharmacology review by Gopichand Gottipati (NDA209885; archived 08/10/2017) for additional information.

Table 45. Description of studies included in the population PK analysis

Study	Description	Dose Regimens (Oral Administration)	Number of Subjects	PK Blood Sampling
AUS-SD-809-CTP-07 (part 1)	A phase 1 study to evaluate the pharmacokinetics of two extended release (ER) formulations of TEV-50717 with and without food compared to tetrabenazine tablets and the pharmacokinetics and dose proportionality of the selected formulation following single and multiple doses.	Formulation A of TEV-50717 tablets 15 mg administered under fasted and fed states.	25 subjects.	At pre-dose, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post dose.
AUS-SD-809-CTP-07 (part 2)	A phase 1 study to evaluate the pharmacokinetics of two ER formulations of TEV-50717 with and without food compared to tetrabenazine tablets and the pharmacokinetics and dose proportionality of the selected formulation following single and multiple doses.	Formulation A of TEV-50717 formulation A under fed state: Single doses of 7.5, 15 and 22.5 mg, or multiple doses of 7.5, 15 and 22.5 mg BID were administered.	24 subjects.	Rich profiles (i.e. at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post dose).on days 1, 4, 10 and 17, and trough on days 7, 8, 9, 13, 14, 15, and 16.
AUS-SD-809-CTP-08	A drug interaction study of TEV-50717 ER and repeated doses of paroxetine.	Single dose of TEV-50717 ER 22.5 mg formulation A (fed state) on treatment days 1 and 11. Co-administration of paroxetine 20 mg QD on days 4 through 12, in the fasted state.	24 subjects.	On days 1 and 11: at pre-dose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours post dose.
SD-809-C-11	A relative bioavailability study of the three dose strengths of TEV-50717 extended release.	A: 6 mg of TEV-50717 ER following a standard test meal. B: 12 mg of TEV-50717 ER following a standard test meal. C: 18 mg of TEV-50717 ER following a standard test meal. D: 24 mg of TEV-50717 ER following a standard test meal.	32 subjects of which 30 completed the treatment.	On day 1 of each period: at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post dose.
SD-809-C-21	A randomized double-blind, placebo- and positive-controlled crossover study to evaluate the effects of single doses of TEV-50717 and tetrabenazine on the corrected QT interval.	A: 12 mg of TEV-50717 plus moxifloxacin placebo and placebo for tetrabenazine. B: 24 mg of TEV-50717 plus moxifloxacin placebo and placebo for tetrabenazine. C: TEV-50717 placebo plus moxifloxacin placebo and placebo for tetrabenazine. D: 400 mg of moxifloxacin plus TEV-50717 placebo and placebo for tetrabenazine. E: 50 mg of tetrabenazine plus moxifloxacin placebo and TEV-50717 placebo. F: Placebo for tetrabenazine plus moxifloxacin placebo and TEV-50717 placebo.	48 patients of which 42 completed the treatment.	At 0.75 h pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 24 hours post dose administration on days 1, 6, 11, 16, 21 and 26.
TV50717-BE-10142	An open-label, randomized, 4-period, 2-treatment, 2-sequence, full replicate crossover study to assess the bioequivalence following administration of a single 12-mg tablet of TEV-50717 (deutetrabenazine) manufactured at two different sites in healthy subjects.	Subjects were randomly assigned to receive reference (R) or test (T) treatments in 1 of the following treatment sequences: RTRT or TRTR, whereby R was one 12 mg tablet of TEV-50717 manufactured at the Norwich site and T was one 12 mg tablet of TEV-50717 manufactured at the Anesta site. Subjects were screened within 28 days before the first dose of study drug (visit 1), followed by a single inpatient stay (visit 2), which includes 4 open-label single-dose treatment periods, and a follow-up visit (visit 3). There was at least a 5-day washout period between administration of study drug in all periods. After at least 10 hours of fasting, subjects were administered TEV-50717.	88 subjects (i.e. 44 subjects per treatment sequence).	Samples were collected immediately (within approximately 30 minutes) before study drug administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hours after each study drug administration.

Study	Description	Dose Regimens (Oral Administration)	Number of Subjects	PK Blood Sampling
TV50717-BA-10146	An open-label, randomized, crossover study to further assess the comparative bioavailability following administration of a single 12-mg tablet of TEV-50717 (deutetrabenazine) manufactured at two different sites in healthy subjects.	Subjects were randomly assigned to receive treatments in 1 of the following treatment sequences: RT or TR, whereby R was one 12 mg tablet of TEV-50717 manufactured at the Norwich site and T was one 12 mg tablet of TEV-50717 manufactured at the Anesta site. Subjects were screened within 28 days before the first dose of study drug (visit 1), followed by a single inpatient stay (visit 2) which includes 2 open-label single-dose administration periods (periods 1 and 2) and a follow-up visit (visit 3). There was at least a 5-day washout period between administrations of study drug in periods 1 and 2. After at least 10 hours of fasting, subjects were administered TEV-50717.	24 subjects (i.e. 12 subjects per treatment sequence).	Samples were collected immediately (within approximately 30 minutes) before study drug administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hours after each study drug administration.
TV50717-BE-10100	An open-label, randomized, crossover study to assess the comparative bioavailability following administration of a single 12-mg tablet of TEV-50717 (deutetrabenazine) manufactured at two different sites in healthy subjects.	Subjects were randomly assigned to receive treatments in 1 of the following treatment sequences: RT or TR, whereby R was one 12 mg tablet of TEV-50717 manufactured at the Norwich site and T was one 12 mg tablet of TEV-50717 manufactured at the Anesta site. Subjects were screened within 28 days before the first dose of study drug (visit 1), followed by a single inpatient stay (visit 2) which includes 2 open-label single-dose administration periods (periods 1 and 2) and a follow-up visit (visit 3). There was at least a 5-day washout period between administration of study drug in periods 1 and 2. After at least 10 hours of fasting, subjects were administered TEV-50717.	24 subjects (i.e. 12 subjects per treatment sequence).	Samples were collected immediately (within approximately 30 minutes) before study drug administration, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hours after each study drug administration.
TV50717-SAD-10132	A randomized, double-blind, placebo-controlled, single ascending dose study to evaluate the electrocardiographic effects, pharmacokinetics, safety, and tolerability of TEV-50717.	Subjects were randomly assigned to receive a treatment sequence which contained periods each containing a dose of TEV-50717 or matching placebo where the appearances of both TEV-50717 and placebo were identical. Subjects in cohorts 1 EM and 1 PM were separately randomized to 1 of 4 sequences that enabled a ratio of TEV-50717 to placebo of 9:3 in each of 3 periods (placebo, 48 mg, 72 mg; 24 mg, placebo, 72 mg; 24 mg, 48 mg, placebo; and 24 mg, 48 mg, 72 mg).	36 subjects.	At pre-dose, and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post dose.
TV50717-BA-10150	An open-label, randomized, 2-part, 3-period, 6-sequence, crossover study to assess the comparative bioavailability of four different 24 mg TEV-50717 once daily formulations following single dose administration compared to a single 12 mg AUSTEDO 1 tablet administered twice 12 hours apart in healthy subjects.	Subjects were randomly assigned to receive 1 of the 6 treatment sequences in part 1 (RT1T2, RT2T1, T1RT2, T1T2R, T2RT1, and T2T1R) or part 2 (RT3T4, RT4T3, T3RT4, T3T4R, T4RT3, and T4T3R) in a 1:1:1:1:1:1 ratio. The treatments were as follows: T1=TEV-50717 QD formulation 1 (test 1) single 24 mg dose. T2=TEV-50717 QD formulation 2 (test 2) single 24 mg dose. T3=TEV-50717 QD formulation 3 (test 3) single 24 mg dose; T4=TEV-50717 QD formulation 4 (test 4) single 24 mg dose. R=AUSTEDO tablet (Reference) two 12 mg tablets 12 hours apart.	48 subjects planned and completed.	Samples were collected immediately (within approximately 30 minutes) before study drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 (immediately prior to administration of the second tablet dose for AUSTEDO), 12.5, 13, 14, 15, 16, 18, 20, 24, 36, 48, 60, 72, and 96 hours after each study drug administration.

Study	Description	Dose Regimens (Oral Administration)	Number of Subjects	PK Blood Sampling
TV50717-BA-10158	An open-label, randomized, 2-Part, 3-period, 6-sequence, crossover study to assess the comparative bioavailability of four different TEV-50717, either 18 or 24 mg, once daily formulations following single dose administration compared to a single 12 mg AUSTEDO 1 tablet administered twice 12 hours apart in healthy subjects.	Subjects were randomly assigned to receive 1 of the 6 treatment sequences in part 1 (R, T2A, T2B; R, T2B, T2A; T2A, R, T2B; T2A, T2B, R; T2B, R, T2A and T2B, T2A, R) or part 2 (R, T4A, T4B; R, T4B, T4A; T4A, R, T4B; T4A, T4B, R; T4B, R, T4A and T4B, T4A, R) in a 1:1:1:1:1:1 ratio. The treatments were as follows: T2A=TEV-50717 QD formulation 2A (test 2A) single 24 mg dose. T2B=TEV-50717 QD formulation 2B (test 2B) single 18 mg dose. T4A=TEV-50717 QD formulation 4A (test 4A) single 24 mg dose. T4B=TEV-50717 QD formulation 4B (test 4B) single 18 mg dose. R=AUSTEDO (reference) two 12 mg tablets 12 hours apart.	48 subjects planned and completed.	Samples were collected immediately (within approximately 30 minutes) before study drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 (immediately prior to administration of the second tablet dose for AUSTEDO), 12.5, 13, 14, 15, 16, 18, 20, 24, 36, 48, 60, 72, and 96 hours after each study drug administration.
SD-809-C-17	A Pilot Study of SD-809 (Deutetrabenazine) in Moderate to Severe Tourette Syndrome.	The starting dose was SD-809 6 mg/day in the morning. The dose of study drug may have been adjusted weekly in increments of 6 mg/day during the titration period to identify a dose level that suppresses tics. The maximum total daily dose of SD-809 at week 5 visit or later was 36 mg (18 mg BID). Dose reductions for intolerability were instructed to be in increments of 6 mg per day.	21 subjects with 9 subjects in the PK sub-study.	Patients enrolled in the PK substudy: at pre-dose, and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 6 hours postdose. For patients not participating in the PK substudy, a single sample was collected at the time of the blood draw for clinical laboratory tests.
TV50717-CNS-30046	A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents.	Subjects randomly assigned to either placebo or active treatment in a 1:1 ratio stratified by age (6 to 11 and 12 to 16 years). Starting total daily dose of 6 mg. Weekly up-titration of total daily dose by 6 mg (except in weeks 3 and 5 for 20-30 kg weight group). at least 40 kg weight group has additional up-titration of 6 mg on day 3. Subjects who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer will stop up-titration earlier than non-impaired subjects. 20-30 kg: week 3, 30-40 kg: week 4, at least 40kg: week 5. Dose adjustments can be made up to and including week 7. After end of titration after week 7 subjects continue to receive their maintenance dose.	100 patients (i.e. 50 per treatment arm).	Sample 1 upon arrival in clinic on week 12, and sample 2 collected 2 to 3 hours after sample 1.
TV50717-CNS-30060	A Well-Controlled, Fixed-Dose Study of TEV 50717 (Deutetrabenazine) for the Treatment of Tics Associated with Tourette Syndrome. The purpose of the study is to determine whether TEV-50717 is effective in the treatment of tics associated with TS in male and female patients between 6 and 16 years of age.	Up-titration scheme over 4 weeks, reaching maintenance dose in week 4. Target daily maintenance dose in low dose TEV-50717 regimen: at least 40 kg 36 (18) mg, 30-40 kg: 24 (12) mg, 20-30 kg: 18 (6) mg. Target daily maintenance dose in high dose TEV-50717 regimen: at least 40 kg 48 (30) mg, 30-40 kg: 36 (18) mg, 20-30 kg: 30 (12) mg. Values in parentheses define total daily doses for subjects who are receiving a strong CYP2D6 inhibitor or who are a CYP2D6 poor metabolizer.	150 patients (i.e. 50 per treatment arm).	Sample 1 upon arrival in clinic on week 8, and sample 2 collected 2 to 3 hours after sample 1.

BID: treatment with AUSTEDO® (twice daily); CYP2D6: cytochrome P450 2D6 enzyme; ER: extended release; PK: pharmacokinetic; QD: treatment with TEV-50717 once daily formulation; TS: Tourette syndrome; EM: extensive metabolizers; PM: poor metabolizers; R: reference; T: test.

[Source: Table 2, Population pharmacokinetic analysis report (PMX-19-11)]

Given the concentrations that were below the lower limit of quantitation (BLOQ) was > 5%, the BLOQ values were handled using M6 method.

The covariates that significantly influenced the PK of α-HTBZ include fed conditions on fraction absorbed, absorption rates and lag time of absorption; fed conditions, CYP2D6 poor and intermediate metabolizer, body weight and strong CYP2D6 inhibitor, paroxetine on clearance (CL/F); body weight and paroxetine on central volume of distribution (Vc/F); body weight and female gender on peripheral volume of distribution (Vp/F). The covariates that significantly influenced the PK of β-HTBZ include fed conditions, CYP2D6 poor and intermediate metabolizer and paroxetine on fraction absorbed; CYP2D6 poor metabolizer and paroxetine on absorption rate constant; fed conditions on lag time of absorption; fed conditions, body weight, CYP2D6 poor and intermediate metabolizer, paroxetine on CL/F; body weight on Vc/F; body weight and paroxetine on Vp/F. The covariates that significantly influenced the PK of parent drug, deutetrabenazine include fed conditions, female gender, CYP2D6 poor metabolizer on relative bioavailability; fed conditions and CYP2D6 poor metabolizer on fraction absorbed; fed conditions, CYP2D6 poor metabolizer and SAD-10132 on absorption rate constant; fed conditions on lag time of absorption; fed conditions, gender and CYP2D6 poor metabolizer on CL/F; female gender on Vc/F.

The population parameter estimates (fixed effects, interindividual variability, parameter-covariate relationship and residual variability) for α-HTBZ are shown in **Table 46**.

Table 46. Population parameter estimates, interindividual variability, residual variability and parameter-covariate relationship of α-HTBZ

Fixed effect parameter	Value	Relative SE, %
CL/F	1720 L/day	1.41
Vc/F	603 L	1.56
Q/F	2110 L/day	1.69
Vp/F	453 L	1.637
ka1	18.1 day^{-1}	6.89
ka2	12.3 day^{-1}	6.58
Tlag1	0.02 days	3.84
Tlag2	0.0214 days	3.98
Fabs	1 fixed	-
Frel0	0.544	0.565
β-CLCYPINHS[a]	-0.6	2.56

[a] due to the use of the stochastic approximation expectation maximization algorithm, time-varying covariates were implemented as model regressors.
α-HTBZ=alpha dihydrodeutetrabenazine; β-CLCYPINHS=impact of strong CYP2D6 inhibitors on CL; CL/F=apparent elimination clearance; F=bioavailability; Fabs=relative oral bioavailability; Frel0=relative fraction absorbed in 0^{th} order process; ka1=absorption rate parameter fast; ka2=absorption rate parameter slow; Q/F=apparent intercompartmental clearance; SE=standard error; Tlag1=lag time fast absorption process; Tlag2=lag time slow absorption process; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution

Inter-individual variability	Value[a]	Relative SE, %	Shrinkage[b], healthy adult subjects, %	Shrinkage[b], TS patients, %
Omega(CL/F)[c]	0.323	2.31	6.1	-22.4
Omega(Vc/F)[c]	0.336	3.7	11.3	52.8
Omega(Q/F)[c]	0.289	3.87	15.3	19
Omega(Vp/F)[c]	0.248	3.84	22.4	44.5
Omega(ka1)[c]	1.29	3	15.5	59.2
Omega(ka2)[c]	1.26	2.93	28.1	56.2
Omega(Tlag1)[c]	0.669	2.87	34.8	73
Omega(Tlag2)[c]	0.688	3.17	23.7	59.9
Omega(Fabs)[d]	0 fixed	-	-	-
Omega(Frel0)[e,f]	0.1 fixed	-	80.1	98.9
Omega(β-CLCYPINHS)[d,f]	0.06 fixed	-	100	97.1

[a] the reported variability was the total variability as a composite of the inter-individual variability and inter-occasion variability.
[b] shrinkage was determined for each indication.
[c] log-normal distribution.
[d] normal distribution.
[e] logit-normal distribution.
[f] due to the use of the stochastic approximation expectation maximization algorithm, a small fixed random effect was ensured when the typical value of the parameter was also estimated.

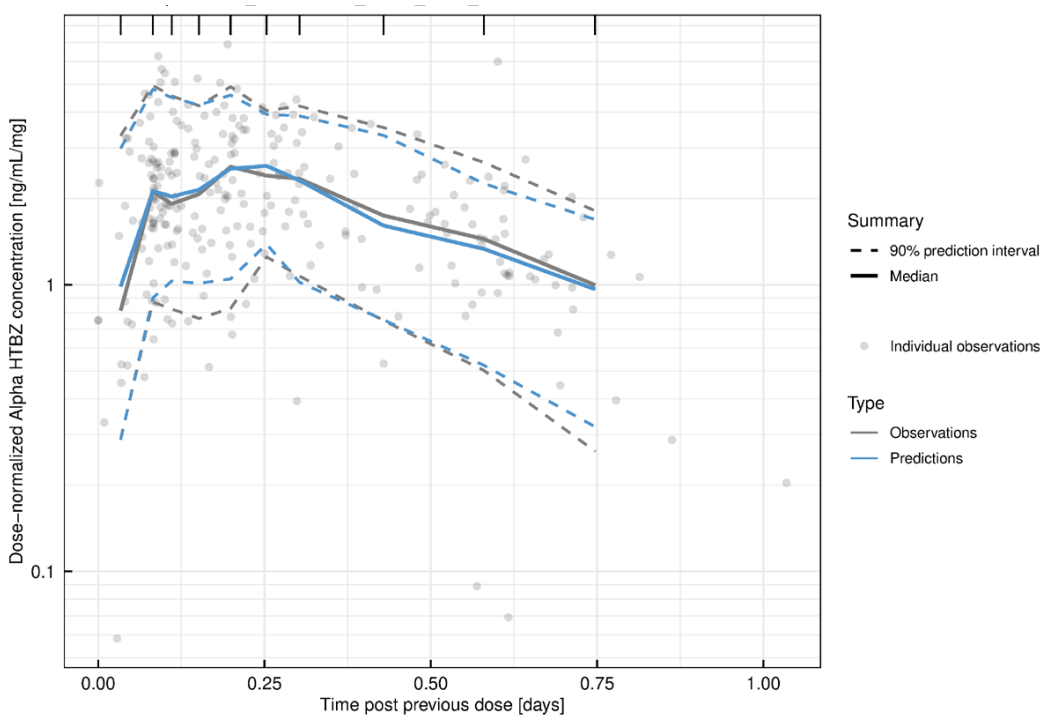
Residual variability	Value	Relative SE, %	Comment
error_ADD1	0.0695	1.59	Additive error (ng/mL), rich
error_PROP1	0.118	0.208	Proportional error (fraction), rich
error_ADD2	1.49	20.7	Additive error (ng/mL), sparse
error_PROP2	0.148	3.44	Proportional error (fraction), sparse

Parameter-Covariate relationship	Value	Relative SE, %	Comment	Equation[a]
beta_Fabs(FED)	0.694	2.15	Fed prandial status on Fabs	$Fabs_{Fed}$ = Fabs x exp(beta_Fabs[FED])
beta_ka1(FED)	-0.0298	372	Fed prandial status on ka1	$ka1_{Fed}$ = ka1 x exp(beta_ka1[FED])
beta_ka2(FED)	0.33	29.2	Fed prandial status on ka2	$ka2_{Fed}$ = ka2 x exp(beta_ka2[FED])
beta_Tlag1(FED)	1.11	5.17	Fed prandial status on Tlag1	$Tlag1_{Fed}$ = Tlag1 x exp(beta_Tlag1[FED])
beta_Tlag2(FED)	1.05	5.52	Fed prandial status on Tlag2	$Tlag2_{Fed}$ = Tlag2 x exp(beta_Tlag2[FED])
beta_CL/F(FED)	0.45	4.96	Fed prandial status on CL/F	CL_{Fed}/F = CL/F x exp(beta_CL/F[FED])
beta_CL/F(CYPPM)	-0.684	7.22	Poor CYP2D6 metabolizer on CL/F	CL_{PM}/F = CL/F x exp(beta_CL/F[CYPPM])
beta_CL/F(CYPIM)	-0.326	13.1	Intermediate CYP2D6 metabolizer on CL/F	CL_{IM}/F = CL/F x exp(beta_CL/F[CYPIM])
beta_CL/F(WTKG)	0.862	4.54	Body weight on CL/F	CL_{WTKG}/F = CL/F x $(WTKG/72.3)^{beta\_CL/F(WTKG)}$
beta_CL/F (PAROX809)	-0.668	10.7	Paroxetine use on CL/F	$CL_{PAROX809}/F$ = CL/F x exp(beta_CL/F[PAROX809])
beta_Vc/F(WTKG)	1.05	6.54	Body weight on Vc/F	Vc_{WTKG}/F = Vc/F x $(WTKG/72.3)^{beta\_Vc/F(WTKG)}$
beta_Vc/F(PAROX809)	-0.199	55.9	Paroxetine use on Vc/F	$Vc_{PAROX809}/F$ = Vc/F x exp(beta_Vc/F[PAROX809])
beta_Q/F(WTKG)	0.904	6.49	Body weight on Q/F	Q_{WTKG}/F = Q/F x $(WTKG/72.3)^{beta\_Q/F(WTKG)}$
beta_Q/F(SEXF_1)	0.148	13.9	Female gender on Q/F	Q_{Female}/F = Q/F x exp(beta_Q/F[SEXF])
beta_Vp/F(WTKG)	1.11	6.97	Body weight on Vp/F	Vp_{WTKG}/F = Vp/F x $(WTKG/72.3)^{beta\_Vp/F(WTKG)}$
beta_Vp/F(SEXF_1)	0.248	9.45	Female gender on Vp/F	Vp_{Female}/F = Vp/F x exp(beta_Vp/F[SEXF])

[a] Fixed effect parameter values
[Source: Tables 4 to 7, Summary of clinical pharmacology]

The dose-normalized plasma concentrations (observed) and model predicted concentrations of α-HTBZ are shown in **Figure 6**.

Figure 6: Dose-normalized plasma concentrations (observed) and the model predicted plasma concentrations of α-HTBZ



[Source: Figure 2, Population pharmacokinetic analysis report (PMX-19-11)]

The population parameter estimates (fixed effects, interindividual variability, parameter-covariate relationship and residual variability) for β-HTBZ are shown in **Table 47**.

Table 47: Population parameter estimates, interindividual variability, residual variability and parameter-covariate relationship of β-HTBZ

Fixed effect parameter	Value	Relative SE, %
CL/F	4540 L/day	2.63
Vc/F	993 L	1.96
Q/F	2390 L/day	3.61
Vp/F	746 L	2.82
ka1	18.2 day^{-1}	3.86
Tlag1	0.0321 days	3.26
ka2	10.1 day^{-1}	6.95
Tlag2	0.019 days	5.71
Fabs	1 fixed	-
Frel0	0.412	0.789
β-CLCYPINHS[a]	-0.588	2.34

[a] due to the use of the stochastic approximation expectation maximization algorithm, a small fixed random effect was ensured when the typical value of the parameter was also estimated.

Inter-individual variability	Value[a]	Relative SE, %	Shrinkage[b], healthy adult subjects, %	Shrinkage[b], TS patients, %
Omega(CL/F)[c]	0.637	2.02	5.6	-26.7
Omega(Vc/F)[c]	0.416	3.71	9.9	-0.6
Omega(Q/F)[c]	0.695	3.88	15.1	8.7
Omega(Vp/F)[c]	0.609	3.7	8.6	16.5
Omega(ka1)[c]	0.817	3.22	16.9	37.4
Omega(Tlag1)[c]	0.585	2.03	33.4	41.8
Omega(ka2)[c]	1.49	2.35	31.9	42.2
Omega(Tlag2)[c]	0.823	1.95	49.6	63
Omega(Fabs)[d]	0 fixed	-	-	-
Omega(Frel0)[e,f]	0.1 fixed	-	80.1	93.6
Omega(β-CLCYPINHS)[d,f]	0.06	-	100	96.7

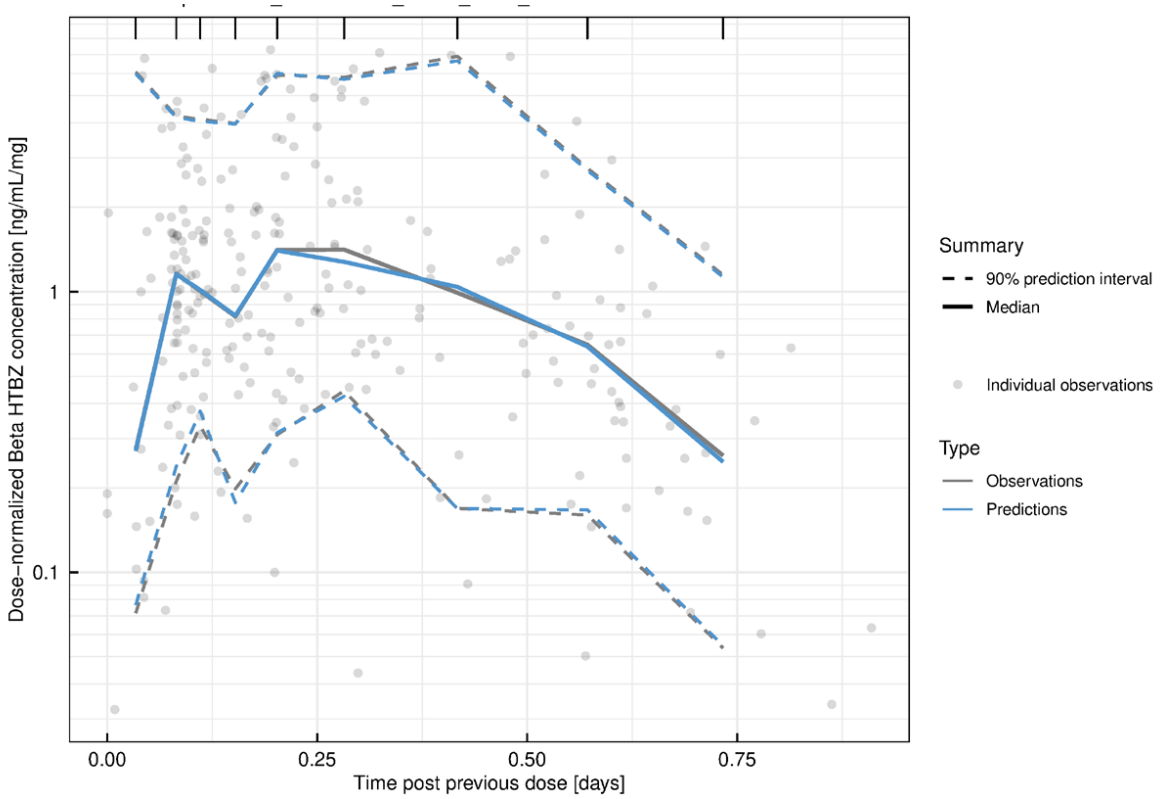
Residual variability	Value	Relative SE, %	Comment
error_ADD1	0.0488	3.93	Additive error (ng/mL), rich
error_PROP1	0.147	0.249	Proportional error (fraction), rich
error_ADD2	0.246	39.5	Additive error (ng/mL), sparse
error_PROP2	0.0691	12.6	Proportional error (fraction), sparse

Parameter-covariate relationship	Value	Relative SE, %	Comment	Equation[a]
beta_Fabs(FED)	0.874	3.6	Fed prandial status on Fabs	$Fabs_{Fed}$ = Fabs x exp(beta_Fabs[FED])
beta_Fabs(CYPPM)	1.4	12.9	Poor CYP2D6 metabolizer on Fabs	$Fabs_{PM}$ = Fabs x exp(beta_Fabs([CYPPM])
beta_Fabs(CYPIM)	0.156	30.4	Intermediate CYP2D6 metabolizer on Fabs	$Fabs_{IM}$ = Fabs x exp(beta_Fabs[CYPIM])
beta_Fabs (PAROX809)	1.03	11.3	Paroxetine use on Fabs	$Fabs_{PAROX809}$ = Fabs x exp(beta_Fabs[PAROX809])
beta_ka1(PAROX809)	0.764	24.3	Paroxetine use on ka1	$ka1_{PAROX809}$ = ka1 x exp(beta_ka1[PAROX809])
beta_ka2(CYPPM)	-0.64	38.8	Poor CYP2D6 metabolizer on ka2	$ka2_{PM}$ = ka2 x exp(beta_ka2[CYPPM])
beta_Tlag1(FED1)	0.967	4.65	Fed prandial status on Tlag1	$Tlag1_{Fed}$ = Tlag1 x exp(beta_Tlag1[FED])
beta_Tlag2(FED)	0.923	6.64	Fed prandial status on Tlag2	$Tlag2_{Fed}$ = Tlag2 x exp(beta_Tlag2[FED])
beta_CL/F(WTKG)	1.23	6.29	Body weight on CL/F	$CL_{WTKG}/F = CL/F \times (WTKG/72.3)^{beta\_CL/F(WTKG)}$
beta_CL/F(FED)	0.622	5.73	Fed prandial status on CL/F	$CL_{Fed}/F = CL/F \times exp(beta\_CL/F[FED])$
beta_CL/F(CYPPM)	-1.8	5.62	Poor CYP2D6 metabolizer on CL/F	$CL_{PM}/F = CL/F \times exp(beta\_CL/F[CYPPM])$
beta_CL/F(CYPIM)	-0.558	11	Intermediate CYP2D6 metabolizer on CL/F	$CL_{IM}/F = CL/F \times exp(beta\_CL/F[CYPIM])$
beta_CL/F(PAROX809)	-1.34	8.96	Paroxetine use on CL/F	$CL_{PAROX809}/F = CL/F \times exp(beta\_CL/F[PAROX809])$
beta_Vc/F(WTKG)	1.23	6.82	Body weight on on Vc/F	$Vc_{WTKG}/F = Vc/F \times (WTKG/72.3)^{beta\_Vc/F(WTKG)}$
beta_Q/F(WTKG)	1.04	16.3	Body weight on on Q/F	$Q_{WTKG}/F = Q/F \times (WTKG/72.3)^{beta\_Q/F(WTKG)}$
beta_Vp/F(WTKG)	1.08	12.5	Body weight on on Vp/F	$Vp_{WTKG}/F = Vp/F \times (WTKG/72.3)^{beta\_Vp/F(WTKG)}$
beta_Vp/F(PAROX809)	-0.497	31.8	Paroxetine use on Vp/F	$Vp_{PAROX809}/F = Vp/F \times exp(beta\_Vp/F[PAROX809])$

[a] Fixed effect parameter values
[Source: Tables 8 to 11, Summary of clinical pharmacology]

The dose-normalized plasma concentrations (observed) and model predicted concentrations of β -HTBZ are shown in **Figure 7**.

Figure 7: Dose-normalized plasma concentrations (observed) and the model predicted plasma concentrations of β -HTBZ



[Source: Figure 4, Population pharmacokinetic analysis report (PMX-19-11)]

The population parameter estimates (fixed effects, interindividual variability, parameter-covariate relationship and residual variability) for deutetrabenazine are shown **Table 48.**

Table 48: Population parameter estimates, interindividual variability, parameter-covariate relationship and residual variabilty of deutetrabenazine

Fixed effect parameter	Value	Relative SE, %
Frel	0.201	5.16
ka1	33.8 day^{-1}	6.38
Tlag1	0.009 days	5.72
ka2	0.99 day^{-1}	2.87
Tlag2	0.00198 days	36.1
CL/F	438000 L/day	4.45
Vc/F	20700 L	7.23
Fabs	1 fixed	-

Inter-individual variability	Value[a]	Relative SE, %	Shrinkage[b], healthy adult subjects, %	Shrinkage[b], TS patients, %
Omega(Frel)[c]	0.924	4.17	13.3	53.1
Omega(Kal)[d]	1.02	5.57	25.5	71.7
Omega(Tlag1)[d]	0.85	3.57	42.3	59.2
Omega(ka2)[d]	0.452	3.49	22.7	25.9
Omega(Tlag2)[d]	2.64	9.34	50	69
Omega(CL/F)[d]	0.614	2.52	1	19.6
Omega(Vc/F)[d]	0.908	3.44	12.8	43.7
Omega(Fabs)[e]	0 fixed	-	-	-

[a] the reported variability was the total variability as a composite of the inter-individual variability and inter-occasion variability.
[b] shrinkage was determined for each indication.
[c] logit-normal distribution.
[d] log-normal distribution.
[e] normal distribution.

Parameter-Covariate relationship	Value	Relative SE, %	Comment	Equation[a]
beta_CL/F(SEXF)	-0.253	18.4	Female gender on CL/F	$CL_{Female}/F = CL/F \times \exp(beta\_CL/F[SEXF])$
beta_CL/F(FED)	0.68	11.1	Fed prandial status on CL/F	$CL_{Fed}/F = CL/F \times \exp(beta\_CL/F[FED])$
beta_CL/F(CYPPM)	-1.2	12.3	Poor CYP2D6 metabolizer on CL/F	$CL_{PM}/F = CL/F \times \exp(beta\_CL/F[CYPPM])$
beta_Vc/F(SEXF)	-0.147	60.6	Female gender on Vc/F	$Vc_{Female}/F = Vc/F \times \exp(beta\_Vc/F[SEXF])$
beta_Frel(SEXF)	0.37	20.4	Female gender on Frel	$Frel_{Female}/F = Frel \times \exp(beta\_Frel[SEXF])$
beta_Frel(FED)	0.232	54.6	Fed prandial status on Frel	$Frel_{Fed}/F = Frel \times \exp(beta\_Fre[FED])$
beta_Frel(CYPPM)	-0.639	37.4	Poor CYP2D6 metabolizer on Frel	$Frel_{PM}/F = Frel \times \exp(beta\_Frel[CYPPM])$
beta_Fabs(FED)	1.53	10.5	Fed prandial status on Fabs	$Fabs_{Fed} = Fabs \times \exp(beta\_Fabs[FED])$
beta_Fabs(CYPPM)	-1.35	17.9	Poor CYP2D6 metabolizer on Fabs	$Fabs_{PM} = Fabs \times \exp(beta\_Fabs[CYPPM])$
beta_ka2(FED)	1.35	5.6	Fed prandial status on ka2	$ka2_{Fed} = ka2 \times \exp(beta\_ka2[FED])$
beta_ka2(S101321)	-1.13	11.6	Study TV50717-SAD-10132 on ka2	$ka2_{TV50717\text{-}SAD\text{-}10132} = ka2 \times \exp(beta\_ka2[S10132])$
beta_ka2(CYPPM1)	-0.62	29.1	Poor CYP2D6 metabolizer on ka2	$ka2_{PM} = ka2 \times \exp(beta\_ka2[CYPPM])$
beta_Tlag1(FED1)	2.08	5.13	Fed prandial status on Tlag1	$Tlag1_{Fed} = Tlag1 \times \exp(beta\_Tlag1[FED])$

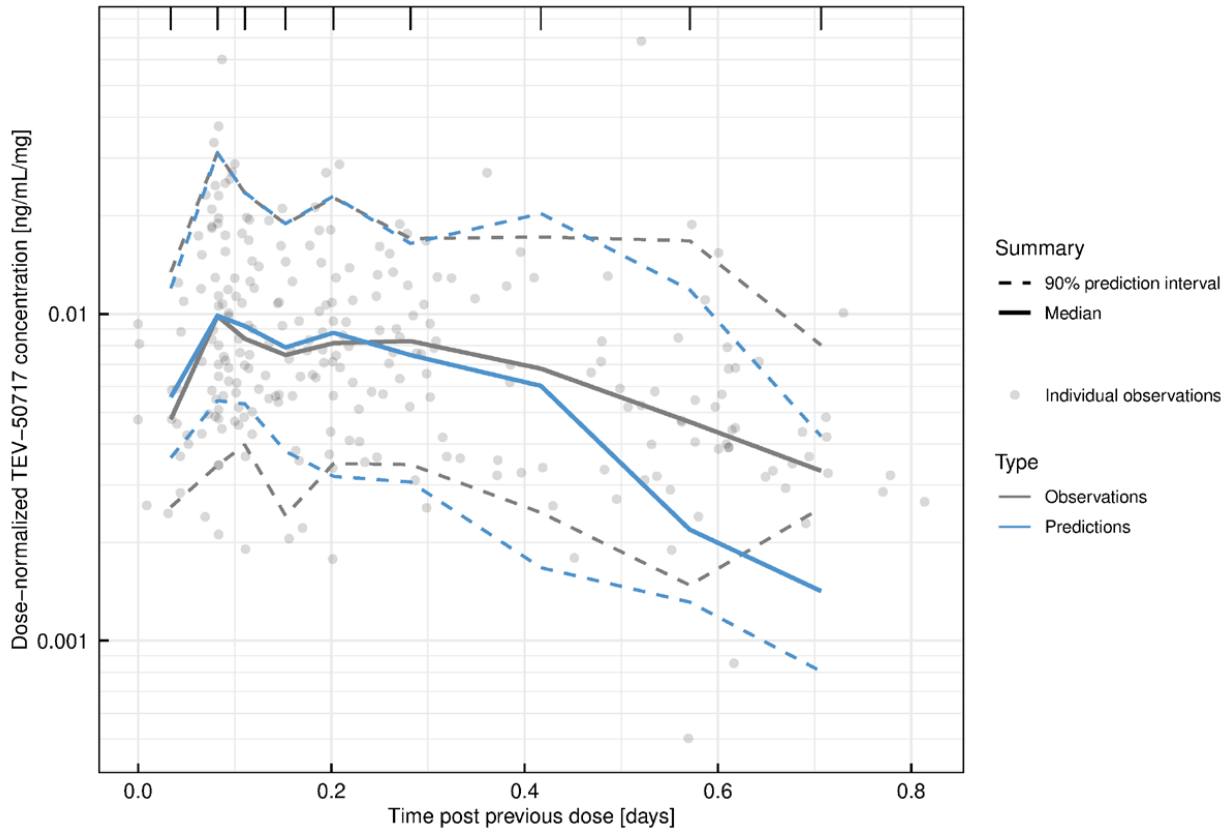
[a] Fixed effect parameter values

Residual variability	Value	Relative SE, %	Comment
error_ADD1	0.00024	24.7	Additive error (ng/mL), rich (low LLOQ)
error_PROP1	0.274	0.468	Proportional error (fraction), rich (low LLOQ)
error_ADD2	0.0141	45.2	Additive error (ng/mL), rich (poor LLOQ)
error_PROP2	0.313	6.23	Proportional error (fraction), rich (poor LLOQ)
error_ADD3	0.035	10.6	Additive error (ng/mL), sparse (patients)

LLOQ=lower limit of quantification; SE=standard error; TS= Tourette syndrome
[Source: Table 12 to 15, Summary of clinical pharmacology]

The dose-normalized plasma concentrations (observed) and model predicted concentrations of β -HTBZ are shown in **Figure 8**.

Figure 8: Dose-normalized plasma concentrations (observed) and the model predicted plasma concentrations of β -HTBZ



[Source: Figure 6, Population pharmacokinetic analysis report (PMX-19-11)]

Table 49: The pharmacokinetic parameters in children (6-11 years) and adolescent patients with TS are shown as three different weight groups (20-30 kg, 30-40 kg, and greater than 40 kg)

Parameter, unit	Analyte	Body weight, geometric mean (CV%[a])		
		20 to <30 kg N=21[b]	30 to <40 kg N=26[c]	≥40 kg N=92
$t_{½}$, h	α-HTBZ	6.94 (19)	7.65 (25.9)	9.38 (27.8)
	β-HTBZ	7.28 (24)	8.56 (31)	8.98 (42)
	TEV-50717	5.13 (18.9)	5.21 (27.9)	5.65 (40.9)
CL/F, L/h	α-HTBZ	49.1 (32.4)	57.9 (49.4)	80.2 (43.7)
	β-HTBZ	118 (53.7)	127 (104)	172 (104)
	TEV-50717	24400 (58.3)	25800 (57)	28600 (65)
Vc/F, L	α-HTBZ	215 (19)	279 (21.6)	472 (27.6)
	β-HTBZ	322(28.6)	397 (51)	652 (43.4)
	TEV-50717	15100 (47.3)	15800 (55.8)	17900 (54.8)
t_{max}, h	α-HTBZ	3.36 (17.6)	3.41 (15.3)	3.55 (16.2)
	β-HTBZ	3.65 (19.7)	4.08 (28.3)	3.86 (24.6)
	TEV-50717	2.2 (19.8)	2.32 (33.5)	2.16 (27.5)
	(α+β)-HTBZ	3.51 (20.3)	3.64 (19.3)[d]	3.66 (20)
$C_{min,ss}$, ng/mL	α-HTBZ	11.2 (65.4)	14.6 (76.6)	16.5 (60.8)
	β-HTBZ	3.63 (117)	6.08 (140)	5.98 (222)
	TEV-50717	0.023 (87.8)	0.0294 (86.9)	0.0393 (87.4)
	(α+β)-HTBZ	15.6 (69.7)	21.2 (92.9)[d]	24.5 (86.2)
$C_{max,ss}$, ng/mL	α-HTBZ	51.1 (42.9)	58.6 (49.8)	54 (38.4)
	β-HTBZ	27.9 (57.9)	32.8 (95.5)	34 (76.1)
	TEV-50717	0.242 (63.4)	0.318 (61.4)	0.376 (55.9)
	(α+β)-HTBZ	79.4 (44.2)	90.9 (61.5)[d]	89.6 (48.1)
$AUC_{0-24,ss}$, ng.h/mL	α-HTBZ	697 (48.3)	838 (52.5)	824 (43.1)
	β-HTBZ	330 (67.6)	426 (102)	441 (103)
	TEV-50717	2.07 (65.8),	2.72 (60.3)	3.27 (58.6)
	(α+β)-HTBZ	1040 (50)	1270 (65.3)[d]	1310 (58.5)

[a] Square root(exponential[variance for log transformed data]-1) × 100.
[b] N=20 for TEV-50717
[c] N=25 for β HTBZ
[d] For TV50717-CNS-30060, patient 060-1602-001, (α+β) HTBZ concentrations were assumed to be equivalent to α-HTBZ concentrations as all β-HTBZ concentrations were below the LLOQ.

[Source: Table 18, Summary of clinical pharmacology]

Clinical Pharmacology Reviewer's Comments: *The PK characterization of deutetrabenazine and its active metabolites (*α-HTBZ and β-HTBZ*) in children (6 to 11 years) and adolescent (12 to 17 years) patients with TS using population PK approach is acceptable. The dose-normalized plasma exposures (Cmax,ss and AUCss) to deutetrabenazine and its active metabolites are relatively similar across the weight groups, 20-30 kg, 30-40 kg, and greater than 40 kg in children and adolescents with TS.*

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/s/

VALERIE A MAGDA
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BERNARD A FISCHER on behalf of TIFFANY R FARCHIONE
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