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Tremor and Other Hyperkinetic Movements

Articles

Deutetrabenazine in Tics Associated with Tourette Syndrome

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Abstract

Background: Deutetrabenazine, an inhibitor of vesicular monoamine transporter type 2 (VMAT2) depletes presynaptic dopamine and is useful in the treatment of hyperkinetic movement disorders. This study explored the safety, tolerability, and preliminary efficacy of deutetrabenazine in adolescents with moderate-to-severe tics associated with Tourette syndrome (TS).

Methods: In this open-label study of 12–18-year-old patients with TS-related tics, deutetrabenazine was titrated up to 36 mg/day over 6 weeks to adequately suppress tics without bothersome adverse effects (AEs), followed by maintenance at optimal dose for 2 weeks. An independent blinded rater assessed tic severity using the Yale Global Tic Severity Scale (YGTSS), which was the primary outcome measure. Secondary outcome measures included the TS Clinical Global Impression (TS-CGI) and TS Patient Global Impression of Change (TS-PGIC).

Results: Twenty-three enrolled patients received deutetrabenazine and had at least 1 post-baseline YGTSS assessment. The mean (SD [standard deviation]) baseline YGTSS Total Tic Severity Score (TTS) was 31.6 (7.9) and had decreased by 11.6 (8.2) points at week 8, a 37.6% reduction in tic severity ($p<0.0001$). The TS-CGI score improved by 1.2 (0.81) points ($p<0.0001$) and the TS-PGIC results at week 8 indicated that 76% of patients were much improved or very much improved compared with baseline. The mean (SD) daily deutetrabenazine dose at week 8 was 32.1 (6.6) mg (range 18–36 mg). One week after withdrawal of deutetrabenazine, the TTS scores increased by 5.6 (8.4) points, providing confirmation of the drug effect. No serious or severe adverse events were reported.

Discussion: The results of this open-label 8-week study suggest that deutetrabenazine is safe and associated with improvement in tic severity in adolescents with TS and troublesome tics.

Keywords: Tics, Tourette syndrome, VMAT2, deutetrabenazine, SD-809

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Conflict of Interest: The authors report no conflict of interest.

Ethics Statement: The study was conducted in accordance with the principles of Good Clinical Practice, and with the FDA guidelines on safety monitoring by Institutional Review Boards for Human Research. Written informed consent by parent/guardian and assent of the adolescent was obtained before study participation. This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki. The authors' institutional ethics committee has approved this study and all patients have provided written informed consent.

Introduction

Tourette syndrome (TS) is a childhood-onset complex neurodevelopmental disorder characterized by multiple motor and phonic tics and a wide range of neurobehavioral problems, including attention deficit with hyperactivity (ADHD) and obsessive–compulsive disorder.[1] The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) defines TS by the presence of multiple motor and phonic tics that persist for at least 1 year and with age of onset prior to 18 years.[2]

The pharmacological treatment of TS consists of antidopaminergic agents and a wide array of other psychotropic medications, and tolerability to these treatments is often compromised by the frequent occurrence of adverse effects (AEs).[3,4] Furthermore, a sizeable number of patients fail to obtain satisfactory relief with conventional medications, and some experience severe disabling tics requiring surgical intervention.[5,6] There is, therefore, an unmet need for safer, more effective pharmacological treatments of tics and behavioral comorbidities associated with TS.

Tetrabenazine, approved in the United States for the treatment of chorea associated with Huntington disease, has shown promise in the treatment of a variety of hyperkinetic movement disorders, including tics associated with TS.[7–9] As a vesicular monoamine transporter, type 2 (VMAT2) inhibitor, tetrabenazine depletes dopamine presynaptically. Although generally effective in reducing abnormal involuntary movements without causing tardive dyskinesia (TD), tetrabenazine is associated with relatively frequent and often intolerable AEs, including somnolence, nausea, depression, insomnia, akathisia, and parkinsonism[8,9] as well as rare episodes of oculogyric reactions and other dystonic responses.[10–12] Tetrabenazine is an immediate-release formulation, and, accordingly, some AEs such as somnolence and akathisia, are often associated with peak concentration immediately after dosing. Furthermore, the active metabolites of tetrabenazine, alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ), have short half-lives, thus requiring repeated dosing of tetrabenazine three times per day or more. The United States Food and Drug Administration (FDA) recommends that patients taking more than 50 mg of tetrabenazine daily are genotyped for polymorphisms in the *CYP2D6* gene, as cytochrome P450 2D6 is involved in the metabolism of α-HTBZ and β-HTBZ. There is, however, little evidence that extensive metabolizers experience fewer AEs than poor metabolizers.[13]

To address the limitations of tetrabenazine, Auspex, a wholly owned subsidiary of Teva Pharmaceutical Industries (Petah Tikva, Israel) has developed deutetrabenazine, a deuterated form of tetrabenazine (also referred to as SD-809 or TEV-50717). Deutetrabenazine is a VMAT2 inhibitor structurally related to tetrabenazine, with two trideuteromethoxy groups (–OCD3) installed at the 9 and 10 positions instead of the two methoxy groups (–OCH3) at the corresponding positions in tetrabenazine. Deuterium placement at these positions attenuates metabolism and thus confer important pharmacokinetic advantages compared with tetrabenazine, including longer half-lives of circulating active metabolites (total [α+β]-HTBZ), reduced metabolic variability and increased the area under the concentration–time curve (AUC) with lower doses and lower peak concentrations without changing the target pharmacology.[14,15] Following oral administration in healthy adults, plasma concentrations of both deutetrabenazine and tetrabenazine are low and transient, suggesting rapid and extensive conversion of both parent drugs to their α-HTBZ and β-HTBZ metabolites, which are then metabolized by CYP2D6 to yield O-desmethyl HTBZ.[15] This reduction in breakdown of the active metabolites results in a substantially lower (about half) dose than tetrabenazine to achieve a similar AUC.[15] As the usual starting dose for tetrabenazine in suppressing tics in TS is 12.5 mg/day,[16] a starting dose of 6 mg of deutetrabenazine was employed in this trial because it was expected to deliver an AUC of total (α+β)-HTBZ that was similar to the 12.5 mg of tetrabenazine but with a lower peak concentration. Because of these pharmacokinetic advantages, deutetrabenazine requires less frequent dosing relative to tetrabenazine and may reduce AEs, particularly drowsiness, often encountered with tetrabenazine, probably related to its high C_{max} within 1 hour after administration. Data in patients receiving deutetrabenazine for the treatment of chorea associated with Huntington disease demonstrated a favorable safety profile with low rates of neuropsychiatric AEs.[17]

Here, we report the results of a phase 1b open-label study of deutetrabenazine in adolescents with troublesome motor and phonic tics. The primary objective of the study is to generate safety and efficacy data about deutetrabenazine in patients with TS that will guide further development of the medication for treatment of tics associated with TS.

Methods

Study design

This was an open-label, prospective study to evaluate the safety and preliminary efficacy of deutetrabenazine for the treatment of troublesome motor and phonic tics in adolescents with TS (ClinicalTrials.gov identifier: NCT02674321). The study was conducted in accordance with the principles of Good Clinical Practice, and with the FDA guidelines on safety monitoring by Institutional Review Boards for Human Research. Written informed consent by the parent/guardian and assent of the adolescent was obtained before study participation.

The study consisted of three periods: a screening period, a treatment period comprising a 6-week titration phase and 2-week maintenance phase, and a 1-week washout period with no treatment. Although our primary objective was to determine safety and dosing of deutetrabenazine in the childhood population, we also sought to obtain information about its efficacy. Throughout the study, an independent rater assessed tic severity with the Yale Global Tic Severity Scale (YGTSS), which was our primary outcome measure. The blinded independent rater did not have knowledge of the patient's clinical care, including medications or reports of AEs. Secondary outcome measures included the TS Clinical Global Impression (TS-CGI) and TS Patient Global Impression of Change (TS-PGIC). As the circulating drug is metabolized by the hepatic enzyme cytochrome P450 (CYP) 2D6, a blinded assessment of the *CYP2D6* genotype was conducted before treatment.

During the screening period, patients underwent a comprehensive evaluation including physical and neurological examinations, assessment of tic severity, medical history, laboratory examination, and 12-lead electrocardiogram (ECG). Patients meeting the selection criteria received 8 weeks of treatment with deutetrabenazine, including a titration period of 6 weeks followed by a maintenance period of 2 weeks. During titration, patients and their parents/guardians interacted weekly with the clinical research staff (clinic visits at weeks 2 and 4, and telephone contacts at weeks 1, 3, 5, and 6) in order to evaluate safety and tolerability, and to identify a dose of deutetrabenazine that adequately reduced tics and was well tolerated. The dose of deutetrabenazine started at 6 mg/day and was increased weekly until there was adequate reduction of tics, the patient experienced a protocol-defined "clinically significant" AE, or the maximal allowable dose was reached. Safety evaluations included monitoring for AEs, assessment of vital signs, and standardized rating scales for depression and suicidal ideation and behavior (Beck Depression Inventory II (BDI-II), the Children's Yale–Brown Obsessive Compulsive Scale (CY-BOCS) and the Columbia Suicide Severity Rating Scale (C-SSRS). At weeks 2 and 4, the YGTSS and TS-CGI were assessed by an independent rater.

During the maintenance period, patients continued to receive the dose established during titration, although dose reductions for treatment-emergent adverse effects, were allowed. Patients returned to the clinic at week 8 for a complete evaluation, including physical and neurological examination, clinical laboratory tests, 12-lead ECG and performance of all rating scales, including the YGTSS and TS-CGI, which were assessed by an independent rater. Patients discontinued deutetrabenazine treatment at the week 8 visit and returned at week 9 for evaluation of safety and tic severity. Patients also had follow-up telephone contact 4 weeks after their last dose of deutetrabenazine to assess adverse events.

Participants

Male and female patients, age 12–18 years, with a diagnosis of TS and troublesome tics were eligible to participate in the study. Eligibility criteria included a DSM-5 diagnosis of TS, manifest motor and/or phonic tics within 3 months before the screening visit, and YGTSS Total Tic Severity Score (TTS) $\geq$19 and TS-CGI score $\geq$4 at screening.

Patients were excluded if they had a neurological disorder other than TS or a serious untreated or undertreated psychiatric illness, such as active suicidal ideation or suicide attempt, depression, schizophrenia, or bipolar disorder at screening. Patients on stable antidepressant therapy for at least 8 weeks before screening could enroll but were excluded if they had received the following medications within 14 days of screening: tetrabenazine, typical and atypical antipsychotics, benzodiazepines, topiramate, metoclopramide, monoamine oxidase inhibitors, levodopa, or reserpine within 21 days. Guanfacine or clonidine within 7 days, reserpine with 21 days, depot neuroleptics, botulinum toxin within 3 months of screening, and participation in an investigational drug or device study within 30 days of screening were prohibited. Other exclusionary criteria were prior treatment with deep brain stimulation for tics, alcohol or substance abuse within 12 months of screening, and a QT interval (corrected by Fridericia's formula) >440 ms on a 12-lead ECG.

Treatment protocol

Deutetrabenazine dosing was individualized for each patient. The starting dose was 6 mg/day and was increased on a weekly basis by 6 mg during the titration period to identify a dose that adequately reduced tics and was well tolerated. Daily doses of 12 mg and higher were administered in two divided doses with food, approximately 10 hours apart during the day. The maximum daily dose of deutetrabenazine was 36 mg/day, less than the 48 mg maximum allowed dose used in studies of deutetrabenazine in an adult population.[17]

Assessments and outcome measures

Efficacy measures included a change from baseline to week 8 in the YGTSS TTS (the primary outcome measure), the TS-CGI, and the TS-PGIC at week 8. The YGTSS evaluates tics during the previous week and has two components: the TTS and the Tic-Related Impairment Score (TIS).[18] The TTS has a total of five domains, number, frequency, intensity, complexity, and interference, each rated on a 0–5 scale for both motor and phonic (vocal) tics (total maximum TTS is 50). The TIS ranges between 0 and 50. Thus the maximum total YGTSS score, or the Global Severity Score (GSS, TTS plus TIS) is 100. The TS-CGI is a 7-point Likert scale that allows clinicians to use all available information to assess the impact of tics on the patient's quality of life and is rated as follows: 1 (normal), 2 (borderline), 3 (mild), 4 (moderate), 5 (marked), 6 (severe), and 7 (extreme).[19] The TS-PGIC is a single-item questionnaire that asks patients to assess their overall condition after initiating therapy. It consists of a 7-point Likert scale, ranging from very much worse (–3) to very much improved (+3).[20] Figure 1 provides a list and timeline of the various assessments performed during the course of the trial.

Safety and tolerability were assessed throughout the study by monitoring AEs, physical and neurological examinations, vital signs, 12-lead ECGs, clinical chemistry and hematology tests, the BDI-II, CY-BOCS, and C-SSRS rating of suicidal behaviors.

Statistical analyses

Since this was an exploratory trial, intended to be used in the design of subsequent studies, no sample power analysis was done. Efficacy analyses were conducted on patients who received at least one dose of the study drug and had at least one post-baseline YGTSS assessment (efficacy population) and were based on observed scores; missing data were not imputed for these analyses. Sensitivity analyses using the last observation carried forward method to impute missing data at week 8 were conducted for efficacy endpoints to assess the robustness of the efficacy data. If a patient's value at week 8 was missing, the most recent non-missing value was carried forward.

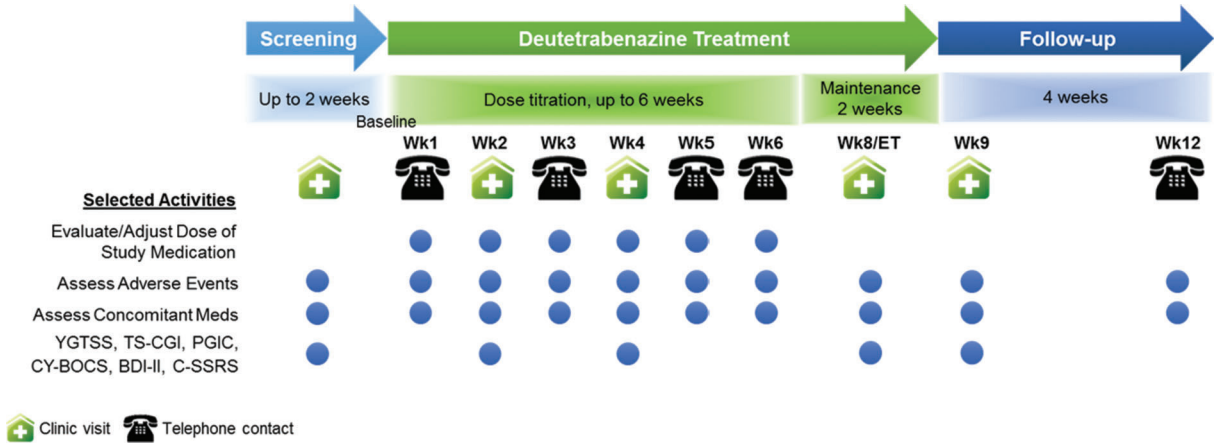

Figure 1. **Study Design.** Timeline of in-person and telephone visits and a list of assessments at each visit. Abbreviations: YGTSS, Yale Global Tic Severity Scale; TS-CGI, Tourette's Syndrome Clinical Global Impression; PGIC, Patient Global Impression of Change (administered at weeks 2, 4, 8, and 9 only), CY-BOCS, Children's Yale–Brown Obsessive–Compulsive Scale; BDI-II, Beck Depression Inventory; C-SSRS, Columbia Suicide Severity Rating Scale.

For YGTSS and TS-CGI analyses, the change from baseline, percentage change from baseline, change from week 8 to week 9, and percentage change from week 8 to week 9 were analyzed using two-sided, one-sample t-tests. The number and percentage of patients in each TS-CGI category were tabulated by visit, including those whose symptoms improved or worsened from baseline. The TS-PGIC data were tabulated by visit without missing data imputation, including the number and percentage of subjects in each rating category by time point. For the TS-PGIC analyses, a two-sided, Wilcoxon-signed rank test was performed at each post-baseline time point to test the null hypothesis that the median score equals zero (no change). Statistical tests were performed at the 0.05 significance level.

Safety analyses were performed on all subjects who received at least one dose of study medication. The overall safety and tolerability of deutetrabenazine was assessed throughout the study by monitoring AEs, and observed changes from baseline to week 8 clinical visits in psychometric evaluations, measures of clinical laboratory parameters, vital signs, neurological examinations, ECG parameters, and the proportion of patients with on-treatment QTcF values >450 ms, >480 ms, and >500 ms.

Results

Participant disposition

A total of 23 patients (17 males), mean (SD [standard deviation]) age 16 (2.3) years were enrolled in the study, received a dose of deutetrabenazine, and had at least one post-baseline YGTSS assessment. Three (13%) patients did not complete the study; one withdrew because of an AE (i.e., non-serious irritability unrelated to treatment) on day 15 of the study, one withdrew for administrative reasons at week 1, and one did not complete the follow-up visit at week 9. There were no poor metabolizers and three patients were ultrarapid metabolizers on the basis of blinded *CYP2D6* genotyping at screening. During the 8-week treatment period, the mean (SD) percent compliance rate was 93.8 (9.4).

Participant characteristics

The mean (SD) baseline TTS was 31.6 (7.92) and the mean (SD) baseline TIS was 34.3 (9.45). The mean (SD) TS-CGI baseline score was 4.7 (0.88), which characterized the presence of moderate to marked tics. At baseline 18 out of 23 (78.3%) patients were receiving concomitant medications. The most frequently prescribed medications were psychostimulants (35%), antidepressants (26%), and non-steroidal anti-inflammatory agents (26%). At the end of titration (week 6), the mean (SD) daily dose of deutetrabenazine was 31.7 mg (7.14 mg). At the end of the treatment period (week 8), 14 patients were dosed at 36 mg, three at 30 mg, one at 24 mg, and three patients were taking 18 mg per day. The mean (SD) daily dose at week 8 was 32.0 mg (6.7 mg). The three patients genotyped as ultrarapid metabolizers, received a daily dose of 36 mg, the maximum allowed dose, possibly suggesting that these rapid metabolizers require a higher dose.

Efficacy

The mean (SD) change in the TTS from baseline to week 8 (primary outcome measure), as assessed by a blinded rater, was 11.6 (8.18) representing a mean (SD) percent reduction of 37.6% (27.15) with 95% CI –49.96 to –25.24 ($p<0.0001$, Figure 2). This reduction in TTS is almost twice the reported clinically meaningful change of 25% by Joen, et al.[21] In our study 61.9% of treated patients achieved this clinically meaningful change. Although the studies or populations are not comparable, this is higher than the figure of 51.3% reported in patients treated with Comprehensive Behavioral Intervention for Tics.[21]

Mean (SD) baseline YGTSS subscores were GSS=66.0 (16.0), Motor Tic Severity Score = 17.4 (3.9), Vocal Tic Severity Score= 14.2 (5.7), and TIS=34.3 (9.4), and were reduced by 36.7%, 34.98%, 44.31%, and 35.3% respectively (all $p<0.0001$, Table 1). Upon withdrawal of the drug, the mean (SD) TTS increased by 5.6 points from week 8 to week 9, supporting the efficacy observed during the 8-week treatment period.

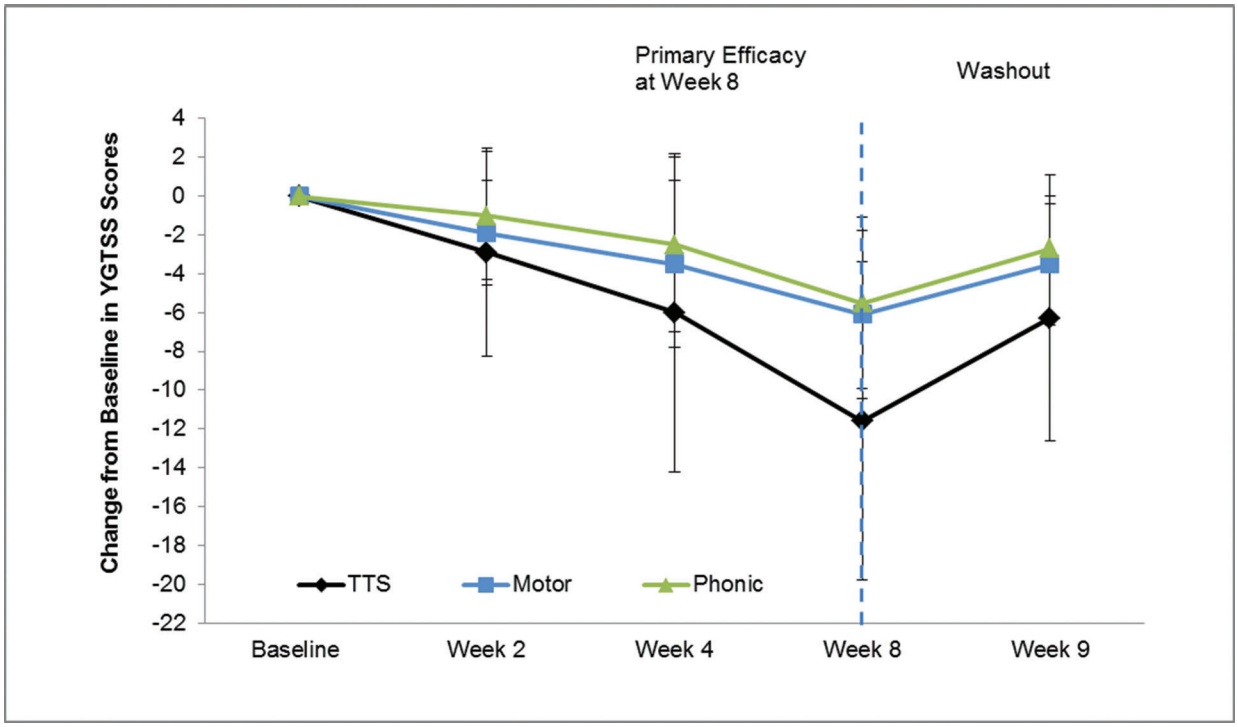

Figure 2. **Changes in Total Tic, Motor, and Phonic Tic Scores over Time.** Primary efficacy scores were change in mean TTS scores at week 8 following 6 weeks of titration and 2 weeks maintenance dosing with deutetrabenazine. The graph illustrates a reduction in TTS, motor and phonic tic mean scores to week 8 (all $p<0.001$). When deutetrabenazine was withdrawn, the total and individual scores increased until the last assessment at week 9. Error bars represent the standard deviations. Abbreviations: YGTSS, Yale Global Tic Severity Scale; TTS, YGTSS Total Tic Score; Motor Tic Score, Motor; Vocal Tic Score, Phonic.

At week 8, treatment with deutetrabenazine resulted in a statistically significant ($p<0.0001$) decrease in the mean (SD) TS-CGI from the observed score at baseline (Table 1). Clinical improvement was observed in the majority of patients, with 85.7% of patients having at least a 1-point score improvement in the TS-CGI from baseline to week 8. At baseline the mean (SD) TS-CGI score was 4.7 (0.88), which represented moderate to marked TS, whereas at week 8, the mean (SD) score observed was 3.6 (1.16), which represented mild to moderate TS (Figure 3). At week 8, all patients noted improvement on the TS-PGIC, with the majority of patients (76.2%) reporting that they were "much improved" or "very much improved" ($p<0.0001$, Figure 4). The mean (SD) deutetrabenazine exposure was 54 (9.3) days (range 15–65 days).

Safety and tolerability

All AEs reported were mild to moderate in severity, and there were no severe AEs, serious AEs, or deaths reported in the study. During the treatment period, which included the titration and maintenance periods, 15 out of 23 (65.2%) patients experienced AEs; the most frequent AEs were fatigue (four; 17%), headache (four; 17%), irritability (three; 13%), somnolence (two; 8%), hyperhidrosis (two; 8%), diarrhea (two; 8%), and nasopharyngitis (two; 8%). One patient reported symptoms consistent with suicidal ideation at week 8 based on the C-SSRS; this event was considered mild and not treatment related by the investigator, who felt that it was more related to the patient's prior history of fluctuating mood; the suicidal thoughts resolved 9 days later without treatment or dose change. One patient withdrew from the study because of irritability that was considered non-serious and not treatment related by the investigator during the titration period. This patient's medical history included receiving risperidone 1 mg for irritability because of ADHD. The risperidone treatment was discontinued prior to study entry and once the patient discontinued from the study, risperidone treatment was reinstated and the irritability resolved. Mean (min–max) QTcF at the screening visit was 398 (354–434) and at week 8 was 402 (379–426).

Discussion

Our phase 1b clinical trial of deutetrabenazine provides evidence that this VMAT2 inhibitor, at doses up to 36 mg/day, may be a safe and effective tic-reducing drug. This conclusion is supported by 37.6% ($p<0.0001$) reduction in the TTS, as assessed by a blinded rater following 8 weeks of deutetrabenazine treatment, and by a limited number of adverse events. In addition, there were significant improvements in the other prespecified efficacy endpoints including TIS, TS-CGI, and TS-PGIC. There was also improvement in the BDI-II and CY-BOCS measures of depression and obsessive–compulsive symptoms. It is not clear why the YGTSS scores 1 week following withdrawal did not return to baseline levels (Figure 2). Although it is possible that the drug may not have completely washed out by week 9, larger and longer studies are needed in the future to address this issue.

Table 1. **Mean Change from Baseline to Week 8**

Assessment		Mean (SD) [95% CI for mean][1]	Change from Baseline At Week 8
TTS	Baseline	31.6 (7.9) [28.2, 35.0]	-11.6 (8.2) [-15.3, -7.8] $p < 0.0001$[2]
	Week 8	20.8 (11.4) [15.6, 25.9]	
TIS	Baseline	34.3 (9.4) [30.3, 38.4]	-11.9 (9.3) [-16.1, -7.7] $p < 0.0001$
	Week 8	22.9 (11.5) [17.6, 28.1]	
GSS	Baseline	66.0 (16.0) [59.0, 72.9]	23.5 (15.7) [-30.6, -16.3] $p < 0.0001$
	Week 8	43.6 (22.0) [33.6, 53.7]	
MTSS	Baseline	17.4 (3.9) [15.7, 19.1]	-6.1 (4.3) [-8.1, -4.1] $p < 0.0001$
	Week 8	11.7 (5.4) [9.2, 14.1]	
VTSS	Baseline	14.2 (5.7) [11.8, 16.7]	-5.5 (4.4) [-7.5, -3.5] $p < 0.0001$
	Week 8	9.1 (6.96) [5.9, 12.3]	
TS-CGI	Baseline	4.7 (0.88) [4.3, 5.1]	-1.2 (0.81) [-1.6, -0.8] $p < 0.0001$
	Week 8	3.6 (1.16) [3.0, 4.1]	
TS-PGIC	-	-	
	Week 8	1 point rating minimally improved n = 5 (23.8%) 2 point rating much improved n = 12 (57.1%) 3 point rating very much improved n = 4 (57.1%) $p < 0.0001$	
BDI-II	Baseline	14.2 (13.9) (0-52)[3]	21; -5.7 (8.0) (-25, -5) -2.7 (5.5) (-23, 0) $p = 0.0352$
	Week 8	8.2 (11.6) (0-33)	
CY-BOCS[4]	Baseline	7.0 (9.2) (0-27)	
	Week 8	4.5 (7.5) (0-25)	

Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression; CI, Confidence Interval; CY-BOCS, Children's Yale–Brown Obsessive Compulsive Scale; GSS, Global Severity Score; max, Maximum; min, Minimum; MTSS, Motor Tic Severity Score; PGIC, Patient Global Impression of Change; SD, Standard Deviation; TIS, Tic-Related Impairment Score; TS, Tourette Syndrome; TTS, Total Tic Severity Score; VTSS, Vocal Tic Severity Score.

[1]Confidence interval based on the t-distribution.

[2]p-values are from two-sided one sample t-tests performed on the change from baseline to week 8 for all endpoints except TS-PGIC for which the Wilcoxon--signed rank test was performed

[3]BDI-II minimum and maximal values provided instead of 95% CI limits

[4]5 patients had baseline values >16 for CY-BOCS total score

n = 23 for baseline measures and n = 21 for Week 8 assessments

Because of the small sample size and short duration of treatment we did not feel it was appropriate or possible to perform correlative analyses to determine if the results were influenced by the presence of various comorbidities, other medications, or by the subjects' *CYP2D6* genotype.

Currently, only haloperidol, pimozide, and aripiprazole are approved by the FDA for the treatment of TS. These neuroleptics, however, have limited usefulness as they are frequently associated with a variety of undesirable AEs, including drowsiness, weight gain, and metabolic syndrome and the potential to cause tardive dyskinesia,[22–24] although the occurrence of TD is rare in adolescents with TS.[25] VMAT2 inhibitors, such as tetrabenazine, which act primarily by depleting presynaptic dopamine rather than by blocking postsynaptic dopamine receptors, have not been documented to cause TD.[26]

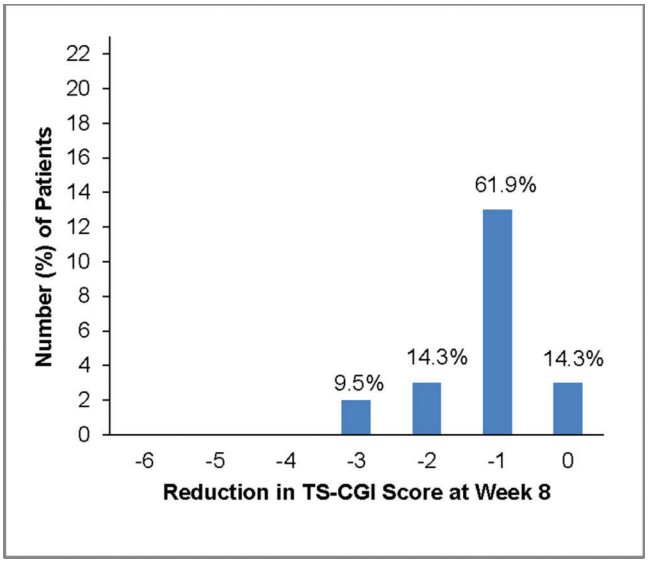

Figure 3. **TS-CGI Score Reductions at Week 8**. Physician ratings of clinical improvement following deutetrabenazine treatment are graphically presented with the number and percentage of patients with score rating reductions by 1, 2, and 3 points occurring between baseline and week 8 TS-CGI assessments. Abbreviations: TS-CGI: Tourette's Syndrome Clinical Global Impression Scale.

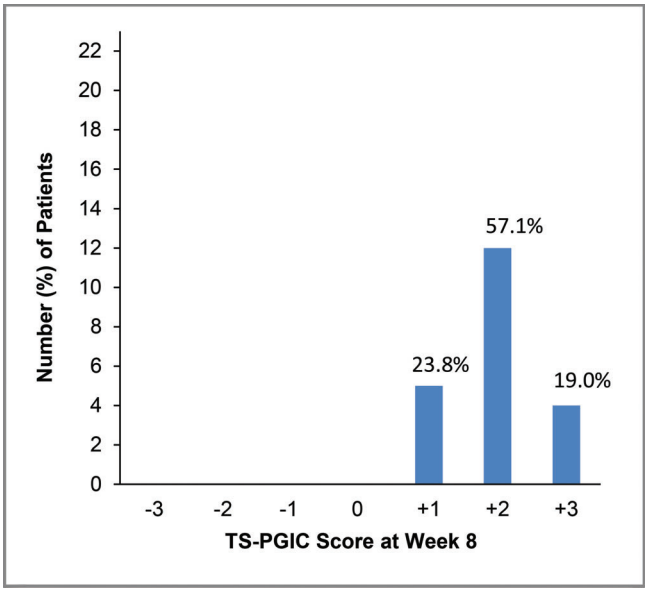

Figure 4. **TS-PGIC Scores at Week 8.** Patient rating in the Tourette Syndrome Patient Global Impression of Change (TS-PGIC).

Indeed, tetrabenazine and novel VMAT2 inhibitors, such as deutetrabenazine and NBI-98854,[27,28] are currently under clinical investigation for the treatment of TD.

The results from our study are similar to the treatment effects demonstrated with tetrabenazine,[7–9], fluphenazine,[29] topiramate,[30] aripiprazole,[31] and other drugs used to treat TS.[1,4,32] Deutetrabenazine was well tolerated (the most common AEs were fatigue, headache, and irritability) and there were no serious AEs, such as depression. Other AEs commonly associated with tetrabenazine, such as parkinsonism and akathisia, were not observed with deutetrabenazine in our study sample. Based on the known pharmacokinetics of deutetrabenazine, it was predicted that the drug would be associated with a relatively low risk of drowsiness (one of the most common AEs associated with tetrabenazine), which tends to correlate with an initial steep rise in blood and brain levels. Indeed in this study, only two (8.7%) of the patients receiving deutetrabenazine experienced somnolence, compared with 36.4% of patients in an open-label retrospective study of patients taking tetrabenazine for TS.[8] Another advantage of deutetrabenazine over tetrabenazine is that it can be administered only twice per day instead of three or more times per day. This should improve medication adherence, especially for children and adolescents. Although this study was relatively short in duration, deutetrabenazine, similar to tetrabenazine, is expected to have a low or no risk of tardive dyskinesia, which is one of the most feared AEs of neuroleptics currently approved by the FDA or used off-label for the treatment of TS.[22–24]

There are several limitations to this study that must be acknowledged, including a small sample size, limited dosing, open-label design, lack of a placebo control, and short duration of treatment relative to natural fluctuations of tics. Because this was a pilot study no inter-rater reliability was conducted, but we ensured that all raters at each center had previous experience at assessing YGTSS scores. Assessments by independent ("blinded") raters may have partially mitigated the lack of a placebo-treated group. Despite these limitations, we believe that the results of this study support further development of deutetrabenazine for the treatment of TS. These preliminary data, while encouraging, should be viewed cautiously and must be validated by a longer, larger double-blind, placebo-controlled trial currently being planned in the United States and Europe.

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