Original Investigation

Effect of Deutetrabenazine on Chorea Among Patients With Huntington Disease
A Randomized Clinical Trial

Huntington Study Group

IMPORTANCE Deutetrabenazine is a novel molecule containing deuterium, which attenuates CYP2D6 metabolism and increases active metabolite half-lives and may therefore lead to stable systemic exposure while preserving key pharmacological activity.

OBJECTIVE To evaluate efficacy and safety of deutetrabenazine treatment to control chorea associated with Huntington disease.

DESIGN, SETTING, AND PARTICIPANTS Ninety ambulatory adults diagnosed with manifest Huntington disease and a baseline total maximal chorea score of 8 or higher (range, 0-28; lower score indicates less chorea) were enrolled from August 2013 to August 2014 and randomized to receive deutetrabenazine (n = 45) or placebo (n = 45) in a double-blind fashion at 34 Huntington Study Group sites.

INTERVENTIONS Deutetrabenazine or placebo was titrated to optimal dose level over 8 weeks and maintained for 4 weeks, followed by a 1-week washout.

MAIN OUTCOMES AND MEASURES Primary end point was the total maximal chorea score change from baseline (the average of values from the screening and day-0 visits) to maintenance therapy (the average of values from the week 9 and 12 visits) obtained by in-person visits. This study was designed to detect a 2.7-unit treatment difference in scores. The secondary end points, assessed hierarchically, were the proportion of patients who achieved treatment success on the Patient Global Impression of Change (PGIC) and on the Clinical Global Impression of Change (CGIC), the change in 36-Item Short Form– physical functioning subscale score (SF-36), and the change in the Berg Balance Test.

RESULTS Ninety patients with Huntington disease (mean age, 53.7 years; 40 women [44.4%]) were enrolled. In the deutetrabenazine group, the mean total maximal chorea scores improved from 12.1 (95% CI, 11.2-12.9) to 7.7 (95% CI, 6.5-8.9), whereas in the placebo group, scores improved from 13.2 (95% CI, 12.2-14.3) to 11.3 (95% CI, 10.0-12.5); the mean between-group difference was −2.5 units (95% CI, −3.7 to −1.3) ($P < .001$). Treatment success, as measured by the PGIC, occurred in 23 patients (51%) in the deutetrabenazine group vs 9 (20%) in the placebo group ($P = .002$). As measured by the CGIC, treatment success occurred in 19 patients (42%) in the deutetrabenazine group vs 6 (13%) in the placebo group ($P = .002$). In the deutetrabenazine group, the mean SF-36 physical functioning subscale scores decreased from 47.5 (95% CI, 44.3-50.8) to 47.4 (44.3-50.5), whereas in the placebo group, scores decreased from 43.2 (95% CI, 40.2-46.3) to 39.9 (95% CI, 36.2-43.6), for a treatment benefit of 4.3 (95% CI, 0.4 to 8.3) ($P = .03$). There was no difference between groups (mean difference of 1.0 unit; 95% CI, −0.3 to 2.3; $P = .14$), for improvement in the Berg Balance Test, which improved by 2.2 units (95% CI, 1.3-3.1) in the deutetrabenazine group and by 1.3 units (95% CI, 0.4-2.2) in the placebo group. Adverse event rates were similar for deutetrabenazine and placebo, including depression, anxiety, and akathisia.

CONCLUSIONS AND RELEVANCE Among patients with chorea associated with Huntington disease, the use of deutetrabenazine compared with placebo resulted in improved motor signs at 12 weeks. Further research is needed to assess the clinical importance of the effect size and to determine longer-term efficacy and safety.

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Huntington disease is a hereditary, progressive, neurodegenerative disease characterized by involuntary movements, cognitive dysfunction, and psychiatric symptoms. Huntington disease is caused by an exon 1 CAG (cytosine-adenine-guanine [amino acid sequence]) trinucleotide expansion in the huntingtin (*HTT*) gene (NC_000004.12; http://www.ncbi.nlm.nih.gov/nuccore/568815594).[1] A prominent Huntington disease symptom is chorea, an involuntary, sudden movement that can affect any muscle and flow randomly across body regions.[2] Chorea can interfere with daily functioning and increase the risk of injury.[3]

Huntington disease treatment is presently focused on symptomatic management. Tetrabenazine is a vesicular monoamine transporter type 2 inhibitor that depletes monoamines, including dopamine, in the central nervous system.[4] It is used worldwide and is the only US Food and Drug Administration-approved therapy for treating chorea associated with Huntington disease. Despite established efficacy, tetrabenazine is subject to variable CYP2D6 metabolism and often requires 3-times-a-day dosing. In addition, there may be some peak concentration-related neuropsychiatric symptoms, such as sedation, fatigue, akathisia, anxiety, or nausea.[5]

Deuterium is a nontoxic form of hydrogen. Based on its increased mass relative to hydrogen, deuterium forms a stronger bond with carbon that requires more energy for cleavage, thus attenuating metabolism.[6] Deuterium substitution in small-molecule drugs does not alter protein binding interactions.[7] Despite the broad interest in using deuterium to improve the pharmacopeia, to date only deuterated tetrabenazine (deutetrabenazine) has progressed to a phase 3 study.[8]

Deutetrabenazine is a vesicular monoamine transporter type 2 inhibitor structurally related to tetrabenazine: deuterium atoms at key positions in the molecule prolong plasma half-life and reduce metabolic variability, without changing target pharmacology.[9] The longer half-life and unique pharmacokinetic profile of deutetrabenazine due to deuterium substitution[9] may enable less frequent and lower daily doses, thus achieving similar systemic exposure with lower peak concentrations and simplified dosing compared with tetrabenazine, resulting in an improved risk-benefit profile. This study tested the efficacy and safety of deutetrabenazine compared with placebo to control chorea while reducing peak concentration adverse effects.

Key Points

Question Does deutetrabenazine safely reduce chorea in patients with Huntington disease?

Findings In this randomized clinical trial that included 90 patients, total maximal chorea mean scores decreased from baseline to maintenance treatment by 4.4 points in the deutetrabenazine group vs 1.9 points in the placebo group, a statistically significant difference.

Meaning Among patients with Huntington disease, the use of deutetrabenazine compared with placebo resulted in improvement in chorea at 12 weeks. Further research is needed to assess the clinical importance of the effect size.

Methods

Patients

Patients were identified and recruited solely through Huntington Study Group investigational sites. Enrolled men and women were ambulatory adults diagnosed with manifest Huntington disease, as indicated by characteristic motor examination features and an expanded *HTT* CAG repeat sequence (≥36). Race was collected for reporting descriptive study demographics; it was self-reported using prespecified fixed categories. Inclusion criteria included a Unified Huntington's Disease Rating Scale (UHDRS), total maximal chorea score of 8 or higher at screening and baseline[10] and a UHDRS total functional capacity score of 5 or higher at screening. The total maximal chorea score is a standardized, reliable chorea assessment based on frequency and severity in 7 body regions, with a range of 0 to 28. The total functional capacity is a 13-point standardized disease staging scale that assesses an individual's ability to perform tasks in 5 functional areas; a score of 5 or higher indicates that patients are in stages I through III and have had a Huntington disease diagnosis for approximately 15 years.

Patients were excluded for serious untreated or undertreated psychiatric illness, such as depression, although patients taking antidepressant therapy and stable could enroll. Patients were excluded if they scored 11 or more on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) or had a history of significant suicidal thoughts or behavior.[11,12] Patients with a prolonged QTc interval, left bundle-branch block, or hepatic or renal impairment were excluded, as were patients with a score of 11 or higher on the Swallowing Disturbance Questionnaire.[13] Patients were also assessed with the Unified Parkinson Disease Rating Scale (UPDRS)[14] speech item and excluded with a score of 3 or higher. (This scale and criterion have been used previously for Huntington disease.[4])

Use of tetrabenazine (within 6 months) was exclusionary, as was use of antipsychotics, metoclopramide, monoamine oxidase inhibitors, levodopa, dopamine agonists, reserpine, amantadine, or memantine within 30 days. Protocol amendment following initiation of the study allowed patients with prior tetrabenazine exposure in order to meet enrollment expectations. Use of drugs that prolong QT intervals other than escitalopram and citalopram were excluded.

All exclusion criteria were developed to minimize confounding factors with study treatment (ie, medications that may alter chorea) and for patient safety due to known effects of vesicular monoamine transporter type 2 inhibitors or neuroleptic agents from previous clinical trials.

Consenting Process

This study was approved by the ethics boards at all involved centers prior to patient enrollment. An independent qualified

clinician assessed all patients for capacity to provide informed consent. Patients or legally authorized representatives provided written informed consent, and patients without capacity provided assent, if required by local regulations. All patients were required to have daily contact with a study partner; patients with more-advanced disease (total functional capacity, 5-7) at screening were required to have a live-in caregiver. The purpose of the study partner or caregiver was to oversee study drug administration, ensure attendance at study visits, and participate in evaluations.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 34 sites in the United States and Canada. Full details of the study protocol can be found in the trial protocol in the Supplement. Throughout the study, the patients, caregivers or study partners, investigators, site personnel, data management staff, and steering committee were blinded to treatment. The safety review committee was blinded to treatment assignment but evaluated treatment groups separately. Patients were titrated to an optimal study drug dose level over 8 weeks, followed by 4 weeks of maintenance therapy. The 12-week treatment period was followed by a 1-week washout. Patients were randomized in a 1:1 ratio to deutetrabenazine or placebo using a computerized randomization algorithm implemented via an interactive web-based randomization system. The randomization was stratified by prior exposure to tetrabenazine (previously exposed vs not previously exposed).

Study Procedures

In-person study visits were conducted at weeks 2, 4, and 6 after initiating therapy, and telephone contacts at weeks 1, 3, 5, 7, and 8. The study drug was started at 6 mg/d and increased weekly by 6 mg/d until chorea was adequately controlled, the patient experienced a clinically significant adverse event, or the 48-mg maximal allowable dose was reached. The study drug was administered in 2 doses daily, approximately 10 hours apart. Dose adjustments were made based on patient and study partner reports of adverse events and chorea control, assessment of safety and efficacy by the investigator, and safety rating scales.

Patients continued to receive their maintenance dose over another 4 weeks, with in-person visits at weeks 9 and 12 for safety and efficacy evaluation and a week-10 telephone contact. Continuation of the maintenance dose was expected, but dose reductions due to adverse events were permitted. All patients discontinued the study drug after the week-12 visit and returned 1 week later for safety and chorea evaluation.

Treatment adherence was assessed by tablet count at every visit while the patient was in the clinic. Percent adherence was calculated as 100 × (number of tablets used/number of tablets expected to be used), for which the number of tablets used was equal to the number of tablets dispensed minus the number of tablets returned. A patient was deemed adherent if he/she had taken 80% to 105% of the expected number of tablets.

Outcomes

The primary efficacy end point was the change in the total maximal chorea score from baseline (defined as the average of values from the screening and day-0 visits) to maintenance therapy (defined as the average of values from the week-9 and week-12 visits). The total maximal chorea score (range, 0-28, lower score indicates less chorea) is the sum of maximal chorea scores for 7 body regions (face, buccal-oral-lingual, trunk, and 4 extremities), each of which is scored on a scale from 0 to 4 (0, absent; 1, slight or intermittent; 2, mild and common or moderate and intermittent; 3, moderate and common; and 4, marked and prolonged).[10] Four key prespecified secondary end points[15] were assessed hierarchically in the following order: Patient Global Impression of Change (PGIC),[16] Clinical Global Impression of Change (CGIC),[17] 36-Item Short Form Health Survey (SF-36)[18] physical functioning subscale score, and Berg Balance Test.[19] The PGIC and CGIC were rated on a 7-point Likert scale ranging from "very much improved" to "very much worse." The PGIC question asked: "With respect to your overall Huntington disease symptoms, how would you describe yourself now compared to immediately before starting study medication?" The CGIC was similarly worded. For PGIC and CGIC, treatment success was defined as "much" or "very much" improved at week 12. The SF-36 and Berg Balance Test were analyzed as changes from day 0 to week 12. According to the most recent American Academy of Neurology guidelines, the minimal clinically important differences for the primary and secondary end points evaluated in this study have not been determined.[20] Additional prespecified efficacy end points included change from baseline to the end of maintenance in the UHDRS total motor score and the percentage change in the total maximal chorea score.

Safety parameters included assessment of adverse events, laboratory tests, vital signs, and electrocardiogram and assessment based on the following scales: UHDRS cognitive, behavioral, and functional scales,[10] Epworth Sleepiness Scale,[21] Columbia Suicide Severity Rating Scale,[22] Swallowing Disturbance Questionnaire,[13] UPDRS speech item,[14] Barnes Akathisia Rating Scale,[23] HADS, and Montreal Cognitive Assessment.[24] These scales were analyzed as changes from day 0 to week 12.

Blinded *CYP2D6* genotyping was performed (Genelex Corp) to assess an association of CYP2D6 metabolism status with deutetrabenazine's efficacy and safety.

Statistical Analysis

The complete statistical analysis plan can be found in the Supplement. All analyses were conducted according to the intention-to-treat model, with all patients included and assigned to the treatment group to which they were randomized. All statistical tests were 2-sided at the 5% level of significance ($P < .05$). Versions 9.2 and 9.3 of the SAS statistical software package were used for all analyses (SAS Institute Inc).

The primary analysis was performed using an analysis of covariance (ANCOVA) model, with the total maximal chorea score change from baseline as the dependent variable, the

treatment group as a factor, and the baseline total maximal chorea score as a covariate. Deutetrabenazine and placebo groups were compared using a 2-sided test at a 5% level of significance. A supportive analysis for the primary end point was carried out using all available data in a mixed model. Secondary end points were analyzed in the prespecified order as above, with any nonsignificant value rendering remaining analyses exploratory rather than confirmatory. Treatment success rates for PGIC and CGIC were compared with Pearson χ^2 tests, and changes in the SF-36 physical functioning score, Berg Balance Test score, and total motor and total maximal chorea score percentage changes were analyzed using ANCOVA models similar to that described for the primary efficacy analysis. Baseline and maintenance values are presented as mean (SDs) or mean 95% (CIs). ANCOVA results are presented as adjusted mean changes and 95% CIs, with the significance levels determined from the adjusted analyses.

For the total maximal chorea, total motor, and Berg Balance Test scores, missing items were imputed if at least 80% of the items for the corresponding score were not missing. The values of the missing items were imputed by carrying forward the most recent previous nonmissing value of the corresponding item, because few missing data were anticipated. There were 2 patients who did not have their total maximal chorea score at maintenance; however, it was determined that the effect of these were minimal to the overall findings. The handling of missing data for individual items of the SF-36 followed the scoring instructions given in the questionnaire manual for the calculation of summary scores. No other missing data were imputed, and only observed data were summarized.

Safety

Safety measures were compared by treatment group using similar ANCOVA models. Adverse events were tabulated and compared using Fisher exact tests.

Sample Size

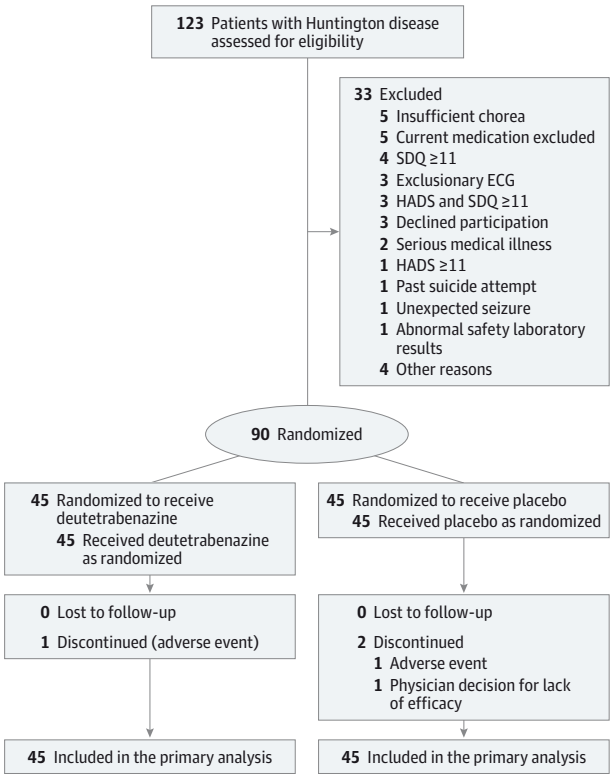
Given a 1:1 randomization and assuming an SD of total maximal chorea score change from baseline to week 12 was equal to 3.7, a sample size of 80 patients gave 90% power to detect a treatment difference of a 2.7-unit change in total maximal chorea score. A 10% dropout rate was anticipated. Although the minimal clinically important difference for UHDRS has not yet been determined, a treatment effect 2.7 units is consistent with the previously published tetrabenazine clinical trial of Huntington disease.[4]

Results

Baseline Comparability

One hundred twenty-three patients were screened, of whom 90 patients enrolled between August 2013 and August 2014 (**Figure 1**). **Table 1** lists baseline characteristics. Five patients had prior tetrabenazine exposure, 3 of whom were in the placebo group. With the exception of a higher Berg Balance Test score in the deutetrabenazine group, the treatment groups were comparable at baseline regarding Huntington disease characteristics, including stage of disease with an overall mean (SD) total functional capacity score of 9.5 (2.1). At screening, 11 patients in the deutetrabenazine group and 13 patients in the placebo group had a total functional capacity of 5 to 7, requiring a live-in caregiver. A total of 87 patients (96.7%) completed the study.

Figure 1. Recruitment and Flow of Study Participants in Trial



HADS, Hospital Anxiety and Depression Scale; ECG, electrocardiogram; and SDQ, Swallowing Disturbance Questionnaire.

Primary Efficacy Outcome

From baseline to maintenance, patients in the deutetrabenazine group had a mean -4.4 (95% CI, -5.3 to -3.6) improvement in total maximal chorea score, whereas the placebo group improved by -1.9 (95% CI, -2.8 to -1.1), with a treatment difference of -2.5 (95% CI, -3.7 to -1.3; $P < .001$; **Figure 2**). Following the washout, chorea returned to baseline levels in both groups. Results using a repeated-measures analysis were similar.

Secondary Outcomes

Twenty-three patients (51%) in the deutetrabenazine group reported treatment success by the PGIC scale, whereas 9 patients (20%) in the placebo group reported treatment success, for a treatment difference of 31.1 (95% CI, 12.4-49.8; $P = .002$). Similarly 19 patients (42%) in the deutetrabenazine group reported treatment success using the CGIC scale

Table 1. Baseline Characteristics by Treatment Group[a]

	Deutetrabenazine (n = 45)	Placebo (n = 45)	All (n = 90)
Patient Demographics			
Age, mean (SD), y	55.4 (10.3)	52.1 (13.4)	53.7 (12.0)
Sex, No. (%)			
Men	22 (49)	28 (62)	50 (56)
Women	23 (51)	17 (38)	40 (44)
White, No. (%)	45 (100)	38 (84)	83 (92)
Education, mean (SD), y	14.8 (2.3)	14.4 (3.0)	14.6 (2.7)
Patient Clinical Characteristics			
CAG repeat length (No.)	43.4 (2.7)	44.3 (4.4)	43.9 (3.7)
BMI	25.4 (4.3)	26.0 (4.6)	25.7 (4.4)
Total UHDRS, mean (SD)			
Functional capacity	9.8 (2.3)	9.2 (2.0)	9.5 (2.1)
Maximal chorea	12.1 (2.7)	13.2 (3.5)	12.7 (3.2)
Motor score	34.1 (13.2)	38.8 (15.2)	36.4 (14.3)
SF-36 physical functioning, mean (SD)	47.5 (10.8)	43.2 (10.2)	45.4 (10.7)
Berg Balance Test, mean (SD)	51.3 (4.5)	48.4 (6.9)	49.9 (6.0)
Barnes Akathisia Rating Scale, median (range)			
Summary score	1 (0-6)	0 (0-7)	0 (0-7)
Global clinical assessment	0 (0-4)	0 (0-4)	0 (0-4)
ESS total score, median (range)	4 (0-14)	5 (0-16)	5 (0-16)
Hospital Anxiety and Depression Scale, median (range)			
Anxiety subscale	2 (0-13)	4 (0-9)	3.5 (0-13)
Depression subscale	1 (0-14)	3 (0-8)	2 (0-14)
Montreal Cognitive Assessment score, mean (range)	23.7 (3.8)	22.8 (4.0)	23.2 (3.9)
Swallowing Disturbance Questionnaire, median (range)	2.5 (0.5-10.5)	4.5 (0.5-11.5)	3.5 (0.5-11.5)
UPDRS Speech, median (range)	1 (0-2)	1 (0-2)	1 (0-2)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAG, cytosine-adenine-guanine (amino acid sequence); ESS, Epworth Sleepiness Scale; SF-36, 36-Item Short Form; UHDRS, Unified Huntington Disease Rating Scale; UPDRS, Unified Parkinson Disease Rating Scale.

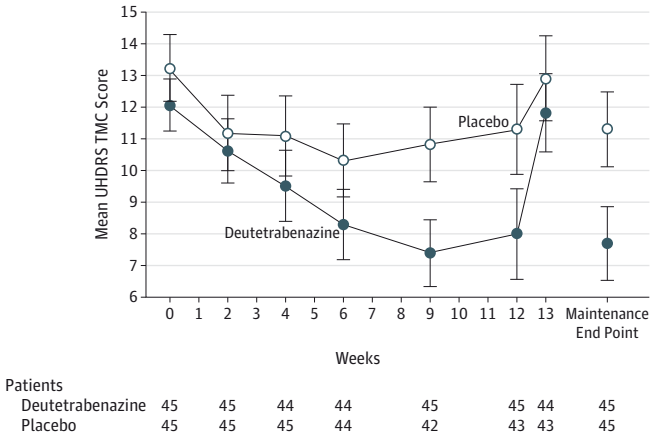
[a] The UHDRS motor assessments are ranked on a scale of 0 (absent) to 4 (severe/prolonged). The summation of scores gives the final rating. The SF-36 physical functioning component is a questionnaire in which an increasing score indicates improvement. The Berg Balance Test is a 14-item survey in which a higher score denotes better balance. The Barnes Akathisia Rating Scale rates are a summary score comprised of objective, subjective, and global clinical assessments, for which higher scores indicate more akathisia and restlessness. The ESS is an 8-item scale to assess daytime sleepiness, for which higher scores indicate increased daytime sleepiness. The Hospital Anxiety and Depression Scale is a 14-item scale (7 items for anxiety and 7 items for depression) with higher scores reflecting greater frequency or severity of symptoms in the preceding week. The Montreal Cognitive Assessment is a screening instrument in which higher scores denote better cognitive function. The Swallowing Disturbance Questionnaire is a 15-item questionnaire in which higher scores indicate greater impairment of swallowing. UPDRS speech is a survey specifically pertaining to speech, with higher scores indicating greater impairment.

vs 6 patients (13%) in the placebo group, for a treatment difference of 28.9 (95% CI, 11.4 to 46.4; P = .002). The SF-36 physical functioning subscale improved by 0.7 (95% CI, -2.0 to 3.4) for deutetrabenazine and worsened by -3.6 (95% CI, -6.4 to -0.8) for the placebo group, for a treatment difference of 4.34 (95% CI, 0.4 to 8.3; P = .03). There was no significant difference in improvement in Berg Balance Test, which improved by 2.2 (95% CI, 1.3-3.1) for deutetrabenazine group and by 1.3 (95% CI, 0.4-2.2) for the placebo group. The mean between-group difference was 1.0 (95% CI, -0.3 to 2.3; P = .14).

Additional Efficacy Outcome Measures

The UHDRS total motor score improved by -7.4 (95% CI, -9.1 to -5.6) in the deutetrabenazine group vs -3.4 (95% CI, -5.1 to -1.6) in the placebo group, for a mean between-group difference of -4.0 points (95% CI, -6.5 to -1.5; P = .002). The majority of this improvement was due to chorea, but the total maximal dystonia score also contributed, as determined by post hoc analysis, with the deutetrabenazine group improving by -0.9 (95% CI, -1.4, to -0.5) points vs placebo group improving by -0.1 (95% CI, -0.6 to 0.4) points, for a between-group difference of -0.8 points (95% CI, -1.5 to -0.1; P = .02). Changes in other UHDRS motor components did not differ significantly between treatment groups, including no significant difference in the changes in the parkinsonism subscore (finger taps; pronation/supination; rigidity; bradykinesia; gait; tandem walking; and retropulsion pull test scores). From baseline to maintenance therapy, the percentage change in the total maximal chorea score improved by -37% (95% CI, -44 to -30) in the deutetrabenazine group vs -16% (95% CI, -23 to -9) improvement in the placebo group, for a between-group difference of -21% (95% CI, -30% to -11%; P < .001).

Figure 2. Total Maximal Chorea Score by Week



Patients								
Deutetrabenazine	45	45	44	44	45	45	44	45
Placebo	45	45	45	44	42	43	43	45

The scale includes the 1-week washout. Baseline value (week 0) is the mean of screening and day 0. Maintenance end point (week 12) is the mean of week-9 and week-12 visits. Error bars indicate 95% CI; TMC, total maximal chorea; and UHDRS, Unified Huntington Disease Rating Scale.

Cognitive, Behavioral, and Functional Measures

Changes from baseline were not significantly different by treatment group for the Montreal Cognitive Assessment (**Table 2**) or UHDRS cognitive, behavioral, or functional measures.

Dosage

The mean (SD) dose at the end of treatment period was 39.7 mg (9.3 mg; range, 12-48 mg) in the deutetrabenazine group and 43.3 mg (7.6 mg; range, 12-48 mg) in the placebo group. Mean (SD) dosage for the 10 deutetrabenazine group patients with impaired CYP2D6 function (poor metabolizers or taking strong CYP2D6 inhibiting medications) was 34.8 mg (3.8 mg; range, 30-42 mg). The overall adherence rates were 94.1% for the placebo group and 95.1% for the deutetrabenazine group.

Safety Outcomes

There were no significant differences between the treatment groups in change from baseline to end of maintenance for the Barnes Akathisia Rating Scale, Epworth Sleepiness Scale, UPDRS speech score, Montreal Cognitive Assessment, or the HADS depression or anxiety subscales. Patients taking deutetrabenazine showed improvement on the SDQ of -1.2 points (95% CI, -2.0 to -0.3); placebo patients worsened by 0.3 points (95% CI, -0.5 to 1.2), for a between-group mean difference of −1.5 (95% CI, -2.7 to -0.3; P = .02). There were no clinically significant differences between treatment groups in changes in laboratory values, vital signs, or electrocardiogram.

The numbers of patients experiencing adverse events overall and within psychiatric and nervous system areas were similar in the deutetrabenazine and placebo groups (**Table 3**). These adverse events were generally mild to moderate and led to dose reduction in 3 patients (6.7%) in each group. The most commonly reported adverse event in the deutetrabenazine group was somnolence, which generally resolved without dose reduction.

Serious adverse events occurred in one patient (2.2%) per group. The patient in the deutetrabenazine group experienced cholecystitis and agitated depression, and patient in the placebo group experienced a chronic obstructive pulmonary disease exacerbation. All events resolved. The study drug was suspended in both cases; these were the only drug suspensions. The numbers of patients reporting depression or agitated depression as an adverse event were not significantly different in the 2 groups. Changes in HADS depression and anxiety scores were not significantly different (Table 2). One patient per group reported suicidal ideation.

The deutetrabenazine group had a weight increase during the treatment period, with a body mass index (BMI) gain of 0.6 (95% CI, 0.3-0.9), compared with loss in the placebo group of -0.1 (95% CI -0.4 to 0.2), for a mean between-group difference of 0.7 (95% CI, 0.3-1.2; P = .002).

Discussion

Deutetrabenazine treatment significantly improved chorea control as measured by the total maximal chorea score, the primary efficacy outcome. Significant improvement was observed in the first 3 prespecified secondary end points, PGIC, CGIC, and SF-36 physical functioning component scales, although no improvement was observed in the Berg Balance Test. In the absence of a well-accepted minimal clinically important difference for total maximal chorea score, this study was powered to detect a 2.7-point difference, which is in line with the pivotal trial of tetrabenazine and consistent with the percentage change in chorea.[4] The observed treatment effect of 2.5 points, the primary end point result, taken together with improvements in patient-centered end points, such as PGIC and SF-36 physical functioning component scales, may be of clinical relevance, although this remains to be determined. The difference in total maximal chorea score associated with deutetrabenazine treatment that was observed in this study is notable given the progressive decline in total maximal chorea score and total motor score that has been previously described as part of the natural history of Huntington disease.[25]

Dystonia is a common motor feature associated with Huntington disease and may have contributed to the significant improvement in total motor score observed with

Table 2. Analyses of Change by Treatment Group

Primary and Secondary Measures[a]	Direction of Favorable Effect	Deutetrabenazine (n = 45)			Placebo (n = 45)			Treatment Difference, Mean (95% CI)	*P* Value[d]
		Baseline[b]	Maintenance[c]	Change From Baseline, Mean (95% CI)[b,d]	Baseline[b]	Maintenance[c]	Change From Baseline, Mean (95% CI)[b,d]		
UHDRS TMC, mean (SD)	–	12.1 (2.7)	7.7 (3.9)	-4.4 (-5.3 to -3.6)	13.2 (3.5)	11.3 (4.1)	-1.9 (-2.8 to -1.1)	-2.5 (-3.7 to -1.3)	<.001
Treatment success at wk 12, No. (%)									
PGIC	+		23 (51)			9 (20)		31.1 (12.4 to 49.8)	.002
CGIC	+		19 (42)			6 (13)		28.9 (11.4 to 46.4)	.002
SF-36, mean (SD)	+	47.5 (10.8)	47.4 (10.3)	0.7 (-2.0 to 3.4)	43.2 (10.3)	39.9 (12.0)	-3.6 (-6.4 to -0.8)	4.3 (0.4 to 8.3)	.03
Berg Balance Test, mean (SD)	+	51.3 (4.5)	53.0 (3.1)	2.2 (1.3 to 3.1)	48.4 (7.0)	50.3 (5.8)	1.3 (0.4 to 2.2)	1.0 (-0.3 to 2.3)	.14
Safety Measures Scores, Mean (SD)									
Barnes Akathisia Rating Scale									
Summary	–	1.4 (1.6)	0.7 (1.2)	-0.6 (-1.0 to -0.3)	1.2 (1.9)	1.0 (1.7)	-0.3 (-0.7 to 0.1)	-0.4 (-0.9 to 0.2)	.19
Global clinical assessment	–	0.8 (1.1)	0.3 (0.7)	-0.4 (-0.6 to -0.2)	0.6 (1.0)	0.5 (0.8)	-0.2 (-0.4 to 0.0)	-0.2 (-0.5 to 0.1)	.22
ESS total score	–	4.6 (3.1)	4.3 (3.9)	-0.4 (-1.4 to 0.5)	5.4 (3.8)	5.2 (3.8)	-0.1 (-1.0 to 0.8)	-0.3 (-1.6 to 1.0)	.62
Hospital Anxiety Depression Scale									
Anxiety	–	3.6 (3.3)	2.6 (3.0)	-1.1 (-1.7 to -0.4)	3.9 (2.7)	3.1 (2.6)	-0.9 (-1.5 to -0.2)	-0.2 (-1.1 to 0.7)	.67
Depression	–	2.1 (2.6)	1.9 (2.3)	-0.5 (-1.1 to 0.2)	3.2 (2.6)	2.9 (2.9)	-0.1 (-0.8 to 0.5)	-0.3 (-1.3 to 0.6)	.46
Montreal Cognitive Assessment total score	+	23.7 (3.8)	23.7 (4.0)	-0.1 (-0.8 to 0.6)	22.8 (4.0)	23.4 (4.4)	0.6 (-0.1 to 1.3)	-0.7 (-1.7 to 0.3)	.15
Swallowing Disturbance Questionnaire	–	3.7 (2.8)	2.6 (2.3)	-1.2 (-2.0 to -0.3)	4.6 (3.1)	4.9 (4.8)	0.3 (-0.5 to 1.2)	-1.5 (-2.7 to -0.3)	.02
UPDRS speech	–	0.7 (0.8)	0.8 (0.7)	-0.0 (-0.2 to 0.1)	1.0 (0.8)	1.0 (0.8)	0.1 (-0.1 to 0.2)	-0.1 (-0.3 to 0.1)	.39

Abbreviations: CGIC, Clinical Global Impression of Change; ESS, Epworth Sleepiness Scale; PGIC, Patient Global Impression of Change; SF-36, 36-Item Short Form; TMC, total maximal chorea score; UHDRS, Unified Huntington Disease Rating Scale; UPDRS, Unified Parkinson Disease Rating Scale.

[a] See Table 1 footnotes for definition of the testing scales.

[b] For UHDRS TMC, the baseline is defined as the mean of screening and day-0 scores.

[c] For UHDRS TMC, *maintenance* is defined as the mean of scores at weeks 9 and 12. For all other measures, *baseline* is defined as the day-0 scores and maintenance as the week-12 scores.

[d] *P* values were obtained from χ^2 tests. Values shown for continuous variables for baseline scores and maintenance scores are reported as mean (SD). Values shown for changes are the least squares means (95% CIs) and *P* values from analysis of covariance models adjusted for the baseline values.

deutetrabenazine treatment compared with placebo. There was no significant improvement in total motor score compared with placebo in the pivotal trial of tetrabenazine,[4] and it is not clear why the deuteration of tetrabenazine might improve dystonia as well as chorea. Future investigation is warranted to confirm the results of these exploratory and post hoc analyses.

The safety profile of deutetrabenazine was similar to placebo in this study. Generally, there was no worsening of depression, although there was one serious adverse event related to agitated depression. Depression is a concern in any patient with Huntington disease, with an increased need to monitor patients taking vesicular monoamine transporter type 2 inhibitors.[26] The deutetrabenazine group did not significantly differ from placebo in the parkinsonism UHDRS motor subscore during 12 weeks of exposure. Tetrabenazine and other antidopaminergic drugs used in chorea treatment did significantly affect this subscore.[27] However, longer-term studies to monitor the development of depression and parkinsonism are needed. The increased incidence of diarrhea with deutetrabenazine treatment, for which there is currently no known cause or association, needs to be closely monitored in future studies.

Patients with more advanced disease were enrolled, and cognitive measures suggested that the existing baseline cognitive impairment did not worsen with deutetrabenazine exposure. Although patients with Huntington disease often lack insight into their own symptoms,[3] patient-reported outcome measures appeared to be reliable in assessing over-

all health and change with intervention. Patients treated with deutetrabenazine reported overall improvement, supported by the secondary outcome measures. Patient-reported outcomes were consistent with clinician-reported outcomes, suggesting that the improvement in motor signs and symptoms associated with deutetrabenazine treatment may be clinically meaningful. Balance difficulty and falls are common problems in patients with Huntington disease. Although there was no improvement in balance, there was also no worsening in the measures of gait, which is meaningful since worsened balance is a potential adverse effect of lower dopamine effect induced by neuroleptics or vesicular monoamine transporter inhibitors. Unified Huntington's Disease Rating Scale functional measures did not differ by treatment group, but meaningful functional change may require longer observation.

Improved swallowing function and reduced chorea may explain weight gain in the deutetrabenazine group. Although the SDQ was normal at baseline, as per inclusion criteria, it improved slightly with deutetrabenazine. Weight loss is a primary Huntington disease symptom that may further worsen motor function; thus, the observed increase in weight patients taking the drug vs placebo is a potential secondary benefit for Huntington disease symptomatic treatments.[28]

Deuterium chemistry offers a strategy for altering drug metabolism while simultaneously preserving pharmacological activity. For instance, the half-life of active metabolites of deutetrabenzine is nearly doubled compared with the half-life of active metabolites of tetrabenazine, allowing it to be administered less frequently and in lower doses while achieving comparable systemic exposure.[9] Reduction in peak concentration adverse effects, such as somnolence and akathisia, and the potential to increase total dose for better efficacy while maintaining tolerability are of particular appeal in treating chorea associated with Huntington disease. In the pivotal tetrabenazine trial that led to its US Food and Drug Administration approval, 44% of patients treated with tetrabenazine had dose-limiting adverse events.[4] These factors may limit use of tetrabenazine and lead to undertreatment of chorea. Peak-concentration adverse effects, monitoring of multiple daily doses, and drug interactions are key concerns in potentially cognitively impaired patients. Deutetrabenazine technology offers promise for other neurological treatments in which such factors limit use or influence drug safety.

Genetic status of *CYP2D6* was not associated with dosing in this study. As expected, poor metabolizers, either through genetics or concomitant medications, were dosed slightly lower. The finding that these patients did not have additional adverse events supports the notion that deutetrabenazine dosing may be managed clinically without reliance on expensive genotyping, but further research with longer-term follow-up is needed to better assess safety.[29,30]

Table 3. Adverse Events by Treatment Group

	No. (%) of Patients[a]	
	Deutetrabenazine (n = 45)	Placebo (n = 45)
Somnolence	5 (11.1)	2 (4.4)
Dry mouth	4 (8.9)	3 (6.7)
Diarrhea	4 (8.9)	0
Irritability	3 (6.7)	6 (13.3)
Insomnia	3 (6.7)	2 (4.4)
Fatigue	3 (6.7)	2 (4.4)
Fall	2 (4.4)	4 (8.9)
Dizziness	2 (4.4)	4 (8.9)
Depression or agitated depression[b]	2 (4.4)	3 (6.7)

[a] Adverse events occurred in 4% or more of patients during the titration and maintenance periods. There were no significant differences between the groups.

[b] Summation of adverse events categorized as depressed or agitated depression.

This study has several important limitations. Huntington disease progresses over years to decades, and the findings in this study should be interpreted in the context of a limited duration of exposure. In addition, this study was not powered for detailed safety assessment. A longer-term open-label safety trial is ongoing to evaluate deutetrabenazine in patients with Huntington disease (NCT01897896). Patients were stratified based on prior tetrabenazine exposure; however, this population was a small proportion of participants. Clinical evaluation is ongoing to evaluate the effect of prior tetrabenazine on deutetrabenazine efficacy and safety in a patient population that more closely represents the general population of patients with Huntington disease. Due to the small number of patients per site, it was not possible to include stratification by site in the randomization algorithm or in the statistical analysis.

Conclusions

Among patients with chorea associated with Huntington disease, the use of deutetrabenazine compared with placebo resulted in improved motor signs at 12 weeks. Further research is needed to assess the clinical importance of the effect size, and to determine longer-term efficacy and safety.

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