Safety of Converting From Tetrabenazine to Deutetrabenazine for the Treatment of Chorea

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IMPORTANCE Tetrabenazine is efficacious for chorea control; however, tolerability concerns exist. Deutetrabenazine, a novel molecule that reduces chorea, was well tolerated in a double-blind, placebo-controlled study.

OBJECTIVES To evaluate the safety and explore the efficacy of conversion from tetrabenazine to deutetrabenazine in patients with chorea associated with Huntington disease (HD).

DESIGN, SETTING, AND PARTICIPANTS In this ongoing, open-label, single-arm study that started on December 21, 2013, 37 patients at 13 Huntington Study Group sites in the United States and Australia who were taking stable doses of tetrabenazine that provided a therapeutic benefit were switched overnight to deutetrabenazine therapy. After week 1, the deutetrabenazine dose was titrated on a weekly basis for optimal chorea control.

INTERVENTIONS Deutetrabenazine administration at a dosage thought to provide comparable systemic exposure to the active metabolites of the prior, stable tetrabenazine regimen.

MAIN OUTCOMES AND MEASURES Safety measures included adverse events (AEs), clinical laboratory tests, electrocardiograms, and validated scales. Changes in the Unified Huntington’s Disease Rating Scale total maximal chorea score and total motor score were efficacy end points.

RESULTS Of the 53 patients with HD screened for the study, 37 ambulatory patients with manifest HD (mean [SD] age, 52.4 [11.5] years; 22 [59%] male and 15 [41%] female; 36 white [97.3%]) were enrolled. Deutetrabenazine was generally well tolerated, with low rates of neuropsychiatric AEs. Safety scales did not reveal subclinical toxicity with deutetrabenazine treatment. Rates of dose reduction or suspension attributable to AEs were also low. Chorea control, as measured by the total maximal chorea score, was maintained at week 1 and significantly improved at week 8 (mean [SD] change from baseline, 2.1 [3.2]; P < .001).

CONCLUSIONS AND RELEVANCE In patients with chorea, overnight conversion to deutetrabenazine therapy provided a favorable safety profile and effectively maintained chorea control.

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Huntington disease (HD) is a hereditary, progressive, neurodegenerative disorder characterized by chorea and other motor symptoms, cognitive dysfunction, and psychiatric symptoms. Up to 90% of patients with HD have chorea that can interfere with daily function and may cause injury.1,2 Tetrabenazine was the first drug approved by the US Food and Drug Administration for chorea associated with HD.3 High peak plasma concentrations and large plasma fluctuations may contribute to the tolerability issues observed in some patients with tetrabenazine use.4 Deutetrabenazine, a novel molecule that contains 6 deuterium atoms in place of 6 hydrogen atoms in specific positions in the tetrabenazine molecule, was approved for treating chorea associated with HD in 2017.5 Clinical evaluation in the First-HD trial found that deutetrabenazine provides significant chorea and motor improvement while maintaining a favorable safety profile when compared with placebo.6 The efficacy and excellent safety profile were attributed to the unique pharmacokinetic profile of deutetrabenazine, which enables comparable systemic exposure at lower doses, lower peak concentrations, and reduced plasma fluctuations.5 The current open-label study evaluated the safety and explored the efficacy of an overnight conversion from tetrabenazine to deutetrabenazine therapy with subsequent optional dose adjustment in patients with HD receiving a stable tetrabenazine regimen for chorea.

Methods

Study Design
This is an ongoing, open-label, single-arm study that started on December 21, 2013, at 13 Huntington Study Group sites in the United States and Australia. In-person study visits were conducted at baseline (day 0), on the last day of tetrabenazine use, and at weeks 1, 4, and 8 after overnight conversion to deutetrabenazine therapy. Telephone consultations were made at weeks 2, 3, and 7. Written approvals from an independent ethics committee or institutional review board were received before the initiation of this study. Western Institutional Review Board was used at all sites except for the following individual institutional review boards: Western Sydney Local Health District Human Research Ethics Committee, University of Alabama Birmingham, Duke University Health System, The Cooper Health System, Vanderbilt University Medical Center, and Rocky Mountain Movement Disorders Center. Institutional review board approval was also obtained at the Chesapeake Institutional Review Board and centrally at the Research Subjects Review Board at the University of Rochester. An independent, qualified health care professional evaluated all patients to determine patient capacity to consent to participate. If patients lacked the capacity to provide informed consent, a legally authorized representative provided written informed consent, in addition to the patients’ provided written assent.

Patients
Patients were eligible if they were ambulatory adults with manifest HD indicated by characteristic motor examination features and an expanded CAG repeat sequence (≥37) and were receiving a stable tetrabenazine regimen for 8 weeks or longer that provided a therapeutic benefit for chorea control. Patients had a total functional capacity score of 5 or higher at screening. The total functional capacity score is a 13-point standardized disease staging scale that assesses an individual’s ability to perform tasks in 5 functional areas: to perform chores, perform activities of daily living, work, manage finances, and live at home. Higher scores indicate earlier disease and better functional status. In early HD, the mean (SD) decline is 0.63 (0.75) points per year.7 Enrolled patients were required to have daily access to reliable caregiver support to oversee study drug administration, ensure attendance at study visits, and provide another level of oversight for safety. Patients with more severe functional impairment as indicated by a total functional capacity score of 5 to 7 at screening were required to have a live-in caregiver.

Patients with serious undertreated psychiatric illness were excluded; however, concomitant stable antidepressant therapy was permitted during the study. Patients with active or past suicidal ideation, thoughts, or behavior were excluded. Patients were excluded if they scored 11 or higher on the Hospital Anxiety and Depression Scale, 11 or higher on the Swallowing Disturbance Questionnaire, or 3 or higher on the dysarthria score of the Unified Parkinson’s Disease Rating Scale. Concomitant use of dopamine receptor antagonists, dopamine agonists, levodopa, reserpine, N-methyl-D-aspartate receptor antagonists, or monoamine oxidase inhibitors within 30 days of screening was also exclusionary.

Dosing
Patients were required to have been receiving a stable tetrabenazine regimen (≥8 weeks) to be eligible. Each patient’s individualized tetrabenazine treatment regimen was determined by his or her primary health care professional independently of this study and before study participation. Masked CYP2D6 (OMIM 124030) genotyping was conducted at screening and remained masked throughout the study. Therefore, subsequent dosing decisions were made without knowledge of the participants CYP2D6 metabolism status. The initial deutetrabenazine daily dose was approximately half the prior tetrabenazine daily dose determined to profile comparable systemic exposure (area under the curve) to active metabolites (eTable in the Supplement). One week after...
Tetrabenazine to Deutetrabenazine Conversion for Chorea Treatment

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Figure 1. Flow of Study Patients

- 53 Assessed for eligibility
- 16 Excluded
- 6 Used exclusionary medication
- 4 Did not meet other inclusion criteria
- 6 Other
- 37 Enrolled
- 1 Withdrew (investigator decision)
- 36 Converted to deutetrabenazine, ongoing participation
- 36 Included in efficacy analysis
- 37 Included in safety analysis

After screening for eligibility, a total of 37 patients were enrolled. Of the 37 patients, 1 patient withdrew and all others continued in the ongoing study.

Results

Baseline Characteristics
A total of 53 patients were assessed for eligibility in the study. Of these, 14 patients were excluded (6 were taking exclusionary medications, 4 did not meet inclusion criteria, 2 had severe suicidal ideation or depression, 1 had abnormal laboratory values, and 1 was excluded for other reasons) and 2 patients declined to participate in the study. Thus, 37 ambulatory patients with manifest HD (mean [SD] age, 52.4 [11.5] years; 22 [59%] male and 15 [41%] female; 36 white [97.3%]) were enrolled (Figure 1). Table 1 lists baseline characteristics, including the baseline TMC scores and TMSs. A total of 26 patients (70%) were being treated with antidepressants at baseline.

Dosage
The initial median deutetrabenazine daily dose was 18.0 mg, approximately half the prior median tetrabenazine daily dose (37.5 mg). After dose adjustment, the median deutetrabenazine daily doses were 30.0 mg at week 4 (n = 37) and 36.0 mg at week 8 (n = 35). Eighteen of 37 participants (49%) were taking the same dose at the week 8 visit as they were taking or assigned at week 4.

Safety Outcomes
A total of 20 patients (54%) reported at least 1 treatment-emergent adverse event (Table 2). No AEs of worsening chorea were reported in this study. Adverse events leading to dose reduction (4 [11%]) or dose suspension (1 [3%]) were observed, and no patient withdrew because of an AE. There were no clinically significant differences in laboratory values, vital signs, body weight, or electrocardiogram findings between baseline and week 8. Two patients (5%) experienced mild depression; the association with deutetrabenazine was rated as possible by the site investigators. There were 9 reported cases of somnolence, of which 6 (67%) were mild; among the remaining 3, 1 case required dose reduction and 1 required dose

Assessments
Safety measures included assessment of adverse events (AEs), clinical laboratory tests, physical and neurologic examinations, vital signs, electrocardiograms, and the following scales: Unified Huntington’s Disease Rating Scale (UHDRS), Hospital Anxiety and Depression Scale, Columbia Suicide Severity Rating Scale, Barnes Akathisia Rating Scale, Montreal Swallowing Disturbance Questionnaire, Unified Parkinson’s Disease Rating Scale dysarthria item, Montreal Cognitive Assessment, and Epworth Sleepiness Scale.

The changes from baseline in the UHDRS total maximal chorea (TMC) score and total motor score (TMS) were evaluated as exploratory efficacy end points. The TMC score is a subset of the TMS; for the TMC and TMS, higher scores indicate greater motor signs.

Safety
Adverse events were tabulated, and treatment-emergent AEs were defined as events that began after initiation of study drug treatment that were not present at baseline or, if present at baseline, that worsened in severity. Two-sided paired t tests were used for descriptive analysis of changes from baseline for the Epworth Sleepiness Scale, Swallowing Disturbance Questionnaire, Unified Parkinson’s Disease Rating Scale dysarthria, and Barnes Akathisia Rating Scale.

Efficacy
Descriptive statistics were conducted for the UHDRS TMC score and TMS for the actual data presented by visit and changes from baseline. Two-sided paired t tests were performed to analyze changes from baseline. Baseline values used for calculating change from baseline for the Epworth Sleepiness Scale, Swallowing Disturbance Questionnaire, Unified Parkinson’s Disease Rating Scale dysarthria, and Barnes Akathisia Rating Scale.

Statistical Analysis
Because this was an open-label safety study, statistical considerations did not determine sample size. All analyses include observed data, with no imputation of missing values. P < .05 (2-sided) was considered statistically significant. Statistical analyses were performed using SAS statistical software (SAS Institute Inc).

overnight conversion to deutetrabenazine, the investigator, in consultation with the patient and caregiver, could begin weekly dose adjustments of deutetrabenazine, if needed, to achieve optimal chorea control. Dose adjustments were made on the basis of assessment of tolerability and chorea control by the investigator. The maximum total daily dose of deutetrabenazine that could be used was 72 mg; however, if the patient was receiving a strong CYP2D6 inhibitor (eg, bupropion, paroxetine, fluoxetine), the maximum total daily dose permitted was 42 mg.
suspension. One patient (3%) experienced a serious AE of dehydration, possibly related to the study drug; the patient continued in the study without change in dose, and dehydration resolved. There were no deaths reported in this study. Dysphagia was not reported as an AE, and Swallowing Disturbance Questionnaire scores did not change significantly during the study.

**Efficacy Outcomes**

The mean (SD) TMS at baseline was 37.7 (18.6), and the mean (SD) TMC score was 12.5 (5.2). The mean (SD) reduction in TMC score from baseline to week 1 was 0.7 (2.6) UHDRS units ($P = .10$) (Figure 2). The mean (SD) reduction in TMC score from baseline to week 4 was 0.6 (3.0) UHDRS units ($P = .02$) at week 1 after dose conversion (Figure 3). The mean (SD) reduction in TMS from baseline to week 8 was 2.1 (5.4) UHDRS units ($P = .02$) at week 1 after dose conversion (Figure 4). Chorea control improved compared with baseline at week 8 (2.1 [3.2]; $P < .001$). The mean (SD) TMS was unchanged compared with baseline at week 4 (1.7 [8.3]; $P = .22$) and week 8 (2.4 [8.7]; $P = .10$).

**Discussion**

Overnight treatment conversion from tetrabenazine 3 times daily to deutetrabenazine twice daily can safely maintain chorea control in patients with HD. Deutetrabenazine therapy was generally well tolerated by patients after the overnight conversion from tetrabenazine. Adherence with a twice-daily medication was excellent and may be attributable to simplified medication regimens compared with existing therapies. The favorable safety profile observed in this study is reflective of the findings in the First-HD study, which supports the hypothesis that deuterium substitution-mediated attenuation of drug metabolism allows for maximal efficacy through dose adjustment while maintaining tolerability in patients with HD. The safety of deutetrabenazine is further highlighted by the low rates of depression and anxiety observed in partici-

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**Table 1. Baseline Characteristics of the Study Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding (N = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient demographic characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>52.4 (11.5)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>15 (41)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>36 (97)</td>
</tr>
<tr>
<td><strong>Patient clinical characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>CAG repeat length</td>
<td>44.5 (3.3)</td>
</tr>
<tr>
<td>Body mass index$^a$</td>
<td>23.9 (4.7)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71.4 (16.6)</td>
</tr>
<tr>
<td>UHDRS total functional capacity</td>
<td>8.3 (2.1)</td>
</tr>
<tr>
<td>UHDRS total maximal chorea</td>
<td>12.5 (5.2)</td>
</tr>
<tr>
<td>UHDRS total motor score</td>
<td>38.5 (18.7)</td>
</tr>
</tbody>
</table>

Abbreviation: UHDRS, Unified Huntington’s Disease Rating Scale.

$^a$ Data are presented as mean (SD) unless otherwise indicated.

$^b$ Calculated as weight in kilograms divided by height in meters squared.

**Table 2. TEAEs Occurring in at Least 4% of Patients**

<table>
<thead>
<tr>
<th>TEAE</th>
<th>No. (%) of Patients (N = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>20 (54)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Fall</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Irritability</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Abbreviation: TEAE, treatment-emergent adverse event.

**Figure 2. Mean Change in Total Maximal Chorea (TMC) Score**

The TMC score was assessed during 8 weeks. The TMC assessments at baseline (blue dotted line) and weeks 1, 4, and 8 are represented for the median daily doses of deutetrabenazine. Error bars represent SEM.

$^a$ $P < .001$.

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**Limitations**

This study was performed with an open-label design without a control group by unmasked site investigators determining chorea and TMSs in unmasked patients who had treatment converted from tetrabenazine to deutetrabenazine, factors that may impart treatment bias. Therefore, all efficacy findings reported in this study should be considered to be exploratory.
Because the deutetrabenazine starting dose was thought to match the systemic active metabolite exposure achieved with the prior tetrabenazine dose, baseline levels of chorea were expected to be maintained but not necessarily improve after the switch to deutetrabenazine therapy. Worsening of chorea was not observed. With optional continued dose adjustments during 8 weeks, chorea control improved. There are a few explanations for continued dose adjustment after 4 weeks in half of the patients. Doses could be adjusted if site investigators and patients thought that the combination of chorea level, effect of chorea on the specific patient, and drug tolerance justified further dose adjustments, up or down, to maximize overall patient status. The TMC score improved at week 8 compared with baseline, suggesting that patients need to be reassessed for tolerability and chorea control after initial treatment conversion and any subsequent dose adjustments. The improvement in chorea raises the possibility that some patients were not able to tolerate higher doses of tetrabenazine or, despite being stable, may have had an incomplete response on tetrabenazine. Patients in either circumstance may be more likely to enroll in this type of study compared with other patients receiving a stable tetrabenazine regimen, creating an ascertainment bias. The starting dose for conversion may also have been too low in some patients.

The patients enrolled in this study were experiencing chorea and receiving tetrabenazine with clinical benefit before treatment conversion. This proof-of-concept study reveals that chorea control can be safely maintained when converting from tetrabenazine to deutetrabenazine, with a favorable safety profile. Change from a nondeuterated to a deuterium substituted compound can achieve treatment goals with fewer doses given across the day, lower total daily dose, and equivalent or potentially improved tolerance, all important considerations in populations with neurodegenerative disease.

Conclusions

The patients enrolled in this study were experiencing chorea and receiving tetrabenazine with clinical benefit before treatment conversion. This proof-of-concept study reveals that chorea control can be safely maintained when converting from tetrabenazine to deutetrabenazine, with a favorable safety profile. Change from a nondeuterated to a deuterium substituted compound can achieve treatment goals with fewer doses given across the day, lower total daily dose, and equivalent or potentially improved tolerance, all important considerations in populations with neurodegenerative disease.
in Neurological Disorders, Neurotherapeutics, Tremor and Other Hyperkinetic Movements, Journal of Parkinson's Disease, and UpToDate. Dr Kostyk reported receiving consulting fees from the National Institutes of Health and the US Food and Drug Administration and has had meeting travel costs covered through the Huntington’s Study Group and Pfizer Pharmaceuticals. Dr Kumar reported receiving personal fees from Teva Pharmaceuticals outside the submitted work. Dr Mallonee reported receiving other support from HSG on behalf of Auspex Pharmaceuticals during the conduct of the study. Dr Oakes reported receiving research support from Auspex for this and another study of SD809 in Huntington disease (HD). Vaccine Inc and Prana Pharmaceuticals for studies in HD, Biogen Inc for a study in Parkinson disease, and the National Institutes of Health for studies in HD and Parkinson disease and personal honoraria from Raptor Pharmaceuticals and Voyager Inc. Dr Sung reported receiving personal fees from Lundbeck Inc. Dr Testa reported receiving grants from the Huntington Study Group, Teva Pharmaceuticals, and the CHDI Foundation and other support from Auspex Pharmaceuticals and Lundbeck Pharmaceuticals outside the submitted work. No other disclosures are reported.

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Role of the Funder/Sponsor: Auspex Pharmaceuticals aided in the design of the study; provided input on the oversight, conduct, and management of the study; played no role in the collection of data but provided oversight with management; was involved with but did not play the primary role in analysis and interpretation of the data; aided in the preparation of the manuscript (figures, references, and formatting) and reviewed content for intellectual property issues; and provided approval of the final draft of the manuscript. The decision to submit the manuscript for publication was based on Huntington Study Group principles with sponsor input through the steering committee.

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REFERENCES


