Indirect Treatment Comparison for Early Efficacy of VMAT2 Inhibitors for Tardive Dyskinesia and Chorea Associated With Huntington's Disease

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INTRODUCTION

- Valbenazine is a uniquely selective vesicular monoamine transporter 2 (VMAT2) inhibitor approved for the treatment of tardive dyskinesia (TD) and chorea associated with Huntington's disease (HD)[1]
- Deutetrabenazine, a deuterated form of an older VMAT2 inhibitor, tetrabenazine, is also approved for TD and HD chorea[2]
- In randomized, double-blind, placebo-controlled (DBPC) trials, efficacy of these medications was demonstrated by significantly greater improvements with active treatment in the following scales:
  - Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1-7) for TD[3-5]
  - Total Maximal Chorea (TMC) score of the Unified Huntington's Disease Rating Scale (UHDRS®) for HD chorea[6,7]
- No head-to-head studies have been conducted to explore potential differences in the effects of these medications for TD or HD chorea
- Previous indirect treatment comparisons (ITCs) using the Bucher method[8] indicated that at the end of DBPC treatment, valbenazine may be more favorable than deutetrabenazine for treatment of TD symptoms, and that at maintenance doses, these medications may have similar efficacy for HD chorea[9,10]
- To evaluate relative efficacy early during treatment, 2 analyses of valbenazine versus deutetrabenazine were conducted using the Bucher ITC method using data from their phase 3 clinical trials for TD and for HD chorea

METHODS

DESIGN OF STUDIES IN TARDIVE DYSKINESIA

- Three randomized DBPC trials in TD were included for analysis: KINECT® 3 (NCT02274558) for valbenazine; and ARM-TD (NCT02195700) and AIM-TD (NCT02291861) for deutetrabenazine[3-5] (**Table 1**)
- The 3 studies were similar in design, with the following notable differences:
  - The valbenazine trial was 6 weeks in duration; the deutetrabenazine trials were 12 weeks
  - The valbenazine study required participants to have moderate to severe dyskinesia at screening (based on qualitative assessment by an external reviewer); participants in the deutetrabenazine studies were required to have an AIMS total score ≥6 at baseline
  - The valbenazine study allowed concomitant anticholinergics; deutetrabenazine studies did not allow the use of strong anticholinergics
- All 3 studies used the AIMS total score (sum of items 1-7) to evaluate efficacy, with scoring based on the assessments of central video raters who were blinded to treatment and the study visit

Table 1. Overview of TD Trials Included in ITC Analysis

Study (Duration)	Treatment Groups, Dosage[a] (n)	Key Eligibility Criteria	Primary Endpoint
Valbenazine			
KINECT 3[3] (6 weeks; fixed dose)	VBZ 40 mg (70) VBZ 80 mg (79) PBO (76)	• Drug-induced TD for ≥3 months • **Moderate to severe dyskinesia (as qualitatively assessed)**[b] • Stable psychiatric status • Stable doses of psychiatric medications allowed • **Concomitant anticholinergics allowed**	AIMS total score change from baseline to Week 6 for VBZ 80 mg
Deutetrabenazine			
ARM-TD[4] (12 weeks; flexible dose)	dTBZ 12-48 mg (48) PBO (49)	• TD diagnosis • **AIMS total score ≥6**[c] • DRBA exposure ≥3 months (≥1 month if ≥60 years) • Stable doses of psychiatric medications allowed • **Strong anticholinergics not allowed**	AIMS total score change from baseline to Week 12
AIM-TD[5] (12 weeks; fixed dose)	dTBZ 12 mg (60) dTBZ 24 mg (49) dTBZ 36 mg (55) PBO (59)	• TD diagnosis • **AIMS total score ≥6**[c] • DRBA exposure ≥3 months (≥1 month if ≥60 years) • Stable doses of psychiatric medications allowed • **Strong anticholinergics not allowed**	AIMS total score change from baseline to Week 12 for dTBZ 36 mg

[a]Dosages reported in total mg/d (valbenazine was given once daily and deutetrabenazine was given twice daily).
[b]Based on qualitative assessment of screening video by an external reviewer.
[c]Investigator-assessed at both screening and baseline and confirmed by blinded central video rater.
AIMS, Abnormal Involuntary Movement Scale; DRBA, dopamine receptor blocking agent; dTBZ, deutetrabenazine; ITC, indirect treatment comparison; PBO, placebo; TD, tardive dyskinesia; VBZ, valbenazine.

DESIGN OF STUDIES IN HUNTINGTON'S DISEASE

- Two randomized DBPC trials in HD were included for analysis: KINECT®-HD (NCT04102579) for valbenazine and FIRST-HD (NCT01795859) for deutetrabenazine (**Table 2**)[6,7]
- Both were 12-week, flexible-dose studies with similar eligibility criteria and primary endpoints based on changes in the TMC score
- In KINECT-HD, valbenazine capsules were administered once daily; valbenazine was initiated at 40 mg and increased in 20-mg increments at the ends of Weeks 2, 4, and 6, as tolerated, to a target daily dose of 80 mg
- In FIRST-HD, deutetrabenazine tablets were administered twice daily; deutetrabenazine was initiated at 6 mg and increased weekly in 6-mg increments until chorea was adequately controlled, a clinically significant adverse event was experienced, or the maximal allowable dose of 48 mg/d was reached

Table 2. Overview of HD Trials Included in ITC Analysis

Study (Duration)	Treatment Groups, Dosage[a] (n)	Key Eligibility Criteria	Primary Endpoint
Valbenazine			
KINECT-HD[6] (12 weeks)	VBZ 40-80 mg (64) PBO (61)	• Diagnosis of motor manifest HD • Expanded *HTT* CAG repeat (≥37) • UHDRS TMC score ≥8 at screening and baseline • UHDRS TFC score ≥5 at screening • Stable psychiatric status	TMC score change from screening/baseline[b] to maintenance[c]
Deutetrabenazine			
FIRST-HD[7] (12 weeks)	dTBZ 6-48 mg (45) PBO (45)	• Diagnosis of motor manifest HD • Expanded *HTT* CAG repeat (≥36) • UHDRS TMC score ≥8 at screening and baseline • UHDRS TFC score ≥5 at screening • Stable psychiatric status	TMC score change from screening/baseline[b] to maintenance[c]

[a]Dosages reported in total mg/d (valbenazine was given once daily and deutetrabenazine was given twice daily).
[b]Average of each participant's scores at screening and baseline.
[c]Average of each participant's scores at Weeks 10 and 12 (valbenazine study) or Weeks 9 and 12 (deutetrabenazine study).
dTBZ, deutetrabenazine; HD, Huntington's disease; ITC, indirect treatment comparison; PBO, placebo; TFC, Total Functional Capacity; TMC, Total Maximal Chorea; UHDRS, Unified Huntington's Disease Rating Scale; VBZ, valbenazine.

BUCHER ITC ANALYSIS FOR TD

- For TD, ITC analysis was conducted in participants who had AIMS assessments at baseline and ≥1 postbaseline visit
- Mean changes from baseline in AIMS total score (sum of items 1-7) at Weeks 2 and 4 were used for analysis (**Table 3**)
  - For valbenazine and placebo, published KINECT 3 data were used[3,11]
  - For deutetrabenazine and placebo, data were digitally extracted from the primary endpoint figures in the ARM-TD and AIM-TD publications[4,5]
- Pooled AIMS total score changes for valbenazine were compared with pooled score changes for deutetrabenazine at both timepoints
  - Valbenazine was taken at doses of 40 or 80 mg/d at both Weeks 2 and 4
  - Deutetrabenazine doses ranged from 12-18 mg/d at Week 2 and 12-30 mg/d at Week 4
- An inverse-variance method was used to pool valbenazine dose groups, to pool treatment groups across deutetrabenazine studies (i.e., data from ARM-TD and AIM-TD were pooled for all receiving deutetrabenazine and all receiving placebo), and to estimate mean changes for AIMS total score

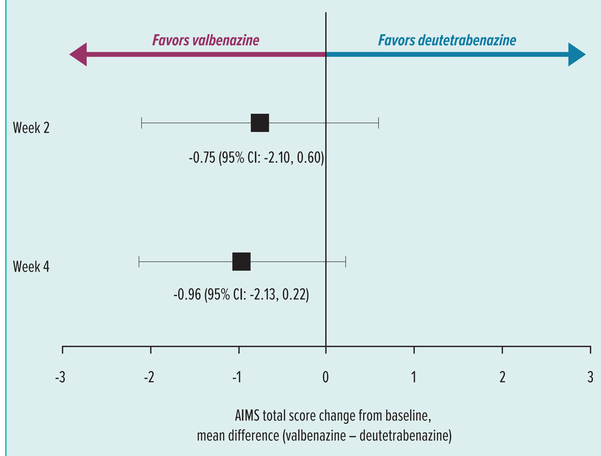
BUCHER ITC ANALYSIS FOR HD CHOREA

- For HD, ITC analysis included participants who had available TMC assessments at screening/baseline (average of each participant's screening and baseline scores) and ≥1 postbaseline visit
- Mean changes in TMC score from screening/baseline at Weeks 2 and 4 were used for analysis (**Table 4**)
  - For valbenazine and placebo, published KINECT-HD data were used[6,11]
  - For deutetrabenazine and placebo, mean changes and 95% confidence intervals (95% CIs) were digitally extracted from the primary endpoint figure in the FIRST-HD publication[7]
- TMC score changes for valbenazine were compared with score changes for deutetrabenazine at both timepoints
  - Valbenazine maximum doses were 40 mg/d at Week 2 and 60 mg/d at Week 4
  - Deutetrabenazine maximum doses were 12 mg/d at Week 2 and 24 mg/d at Week 4
- An inverse variance method was used to estimate the mean changes for deutetrabenazine versus placebo

RESULTS

- In the ITC analysis for early efficacy in TD, AIMS total score improvement numerically favored valbenazine over deutetrabenazine at both Weeks 2 and 4 (**Figure 1**)

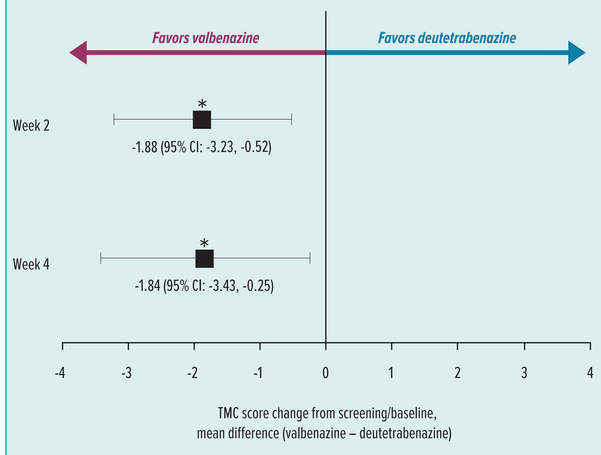
Figure 1. Mean Difference Between Valbenazine and Deutetrabenazine in AIMS Total Score Change From Baseline



Valbenazine was taken at doses of 40 or 80 mg/d (pooled) at both Weeks 2 and 4; deutetrabenazine doses ranged from 12-18 mg/d at Week 2 and 12-30 mg/d at Week 4.
AIMS, Abnormal Involuntary Movement Scale.

- In the ITC for early efficacy for HD chorea, TMC score improvements from screening/baseline significantly favored valbenazine over deutetrabenazine at both Week 2 (with initial 40-mg dose for valbenazine) and Week 4 (**Figure 2**)

Figure 2. Mean Difference Between Valbenazine and Deutetrabenazine in TMC Score Change From Screening/Baseline



Maximum daily doses for valbenazine were 40 mg (Week 2) and 60 mg (Week 4); maximum daily doses for deutetrabenazine were 12 mg/d (Week 2) and 24 mg/d (Week 4).
TMC, Total Maximal Chorea.

CONCLUSIONS

- In the absence of head-to-head trial data, comparisons of relative efficacy using the Bucher ITC method can help inform treatment decisions
- This ITC analysis indicated numerically favorable results for valbenazine versus deutetrabenazine for early improvement of TD, based on AIMS total score changes at Weeks 2 and 4
- It also indicated significantly favorable results for valbenazine versus deutetrabenazine for early improvement of HD chorea, based on TMC score changes at Weeks 2 and 4
- For HD chorea, the ITC results also suggest that the corresponding maximum doses of valbenazine at those time points (40 and 60 mg, respectively) reduce chorea among most patients with HD; in contrast, a 2- to 4-week timeframe might not be sufficient for patients to reach an efficacious dose with deutetrabenazine
- The initial doses of these 2 medications may contribute to differences in early efficacy; valbenazine was initiated at a therapeutic dose of 40 mg/d in both the TD and HD studies, while deutetrabenazine was initiated at 12 mg/d (TD studies) or 6 mg/d (HD study) and participants did not have the opportunity to reach a therapeutic dose (24 mg/d) until Week 4 or later
  - Per the deutetrabenazine prescribing information, deutetrabenazine is initiated at 12 mg/d for HD chorea in clinical practice[2]
- Early symptomatic improvements may demonstrate the necessity of the medication to the patient, potentially improving treatment adherence and willingness to continue on a prescribed regimen[12,13]
- Thus, magnitude of effect and time needed to reach an effective dose are important considerations when choosing a medication to treat the hyperkinetic movement disorders of TD or HD chorea

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