Clinical Efficacy of Valbenazine and Deutetrabenazine for the Treatment of Tardive Dyskinesia: Indirect Treatment Comparison of Randomized Controlled Trials

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INTRODUCTION

- Tardive dyskinesia (TD) is a persistent and often irreversible movement disorder associated with prolonged exposure to antipsychotics and other dopamine receptor blocking agents[1]
- The efficacy of valbenazine and deutetrabenazine in the treatment of TD in adults has been demonstrated in well-controlled clinical trials in which both drugs were significantly superior to placebo at the end of double-blind treatment[2-5]
- However, no head-to-head studies have been conducted to explore the potential differences in the effect of these medications on TD
- This study utilized the Bucher indirect treatment comparison (ITC) method[6] to assess the relative efficacy of valbenazine and deutetrabenazine using pooled data from double-blind, placebo-controlled studies

METHODS

- Four randomized, double-blind, placebo-controlled studies (valbenazine: KINECT 2 [NCT01733121] and KINECT 3 [NCT02274558]; deutetrabenazine: ARM-TD [NCT02195700] and AIM-TD [NCT02291861]) were identified from a systematic search of PubMed and Embase and included in the analysis (**Table 1**)
- Overall, the studies were similar in design, with the following notable differences:
  - Valbenazine trials were 6 weeks in duration; deutetrabenazine trials were 12 weeks
  - Participants in the deutetrabenazine studies were required to have an Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1-7) ≥6 at baseline, while the valbenazine studies required participants to have moderate to severe dyskinesia at screening (based on qualitative assessment by an external reviewer)
  - Valbenazine studies allowed concomitant anticholinergics; deutetrabenazine studies did not allow use of strong anticholinergics
- In all studies, efficacy analyses were conducted in participants who had ≥1 available post-baseline AIMS assessment; additionally, all AIMS scoring was conducted by blinded central video raters

Table 1. Study Design of Valbenazine and Deutetrabenazine Trials Included in the ITC Analysis

Study (Duration)	Treatment Groups, Dosage[a] (n)	Key Eligibility Criteria/Methodology	Efficacy Outcomes
Valbenazine			
KINECT 2[2] (6 weeks)	Valbenazine 25-75 (45) Placebo (44)	• 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 CFB AIMS 50% response CGIC response
KINECT 3[3] (6 weeks)	Valbenazine 40 (52) Valbenazine 80 (61) Placebo (66)	• 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 CFB AIMS 50% response CGIC response
Deutetrabenazine			
ARM-TD[4] (12 weeks)	Deutetrabenazine 12-48 (48) Placebo (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 CFB AIMS response[d] CGIC response
AIM-TD[5] (12 weeks)	Deutetrabenazine 12 (60) Deutetrabenazine 24 (49) Deutetrabenazine 36 (55) Placebo (58)	• 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 CFB AIMS 50% response CGIC response

[a]Dosages reported in total mg/day (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.
[d]Reported in Jimenez-Shahed et al.[7]
AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; CGIC, Clinical Global Impression of Change; DRBA, dopamine receptor blocking agent; ITC, indirect treatment comparison.

BUCHER ITC EFFICACY OUTCOMES

- Efficacy outcomes included mean change from baseline in AIMS total score (sum of items 1-7) and AIMS response (≥50% total score improvement from baseline)
  - To derive deutetrabenazine timepoints that were comparable to the valbenazine 6-week timepoint, AIMS mean changes from baseline were extracted from Week 6 (ARM-TD) and Week 8 (AIM-TD) using a plot digitizer
- Valbenazine and deutetrabenazine were compared by dosage using data from KINECT 3 (valbenazine 40 mg or 80 mg, Week 6) and AIM-TD (deutetrabenazine 24 mg or 36 mg, Week 8 or Week 12)
- Pooled data for valbenazine (KINECT 2/3, 25-80 mg) and deutetrabenazine (AIM-TD/ARM-TD, 12-48 mg) were compared at Week 6 (valbenazine) versus Week 6/8 (deutetrabenazine) (**Table 2**)
  - Since efficacy was not demonstrated for the lowest dosage in AIM-TD (12 mg), a more conservative analysis was conducted in which this dose was excluded from the deutetrabenazine dataset

Table 2. Studies and Doses Used for the ITC Method

AIMS Outcome	Valbenazine			Deutetrabenazine		
	Studies	Doses	Timepoint	Studies	Doses	Timepoint
Comparisons by Dose						
Mean change from baseline	KINECT 3	40 mg	6 weeks	AIM-TD	24 mg 36 mg	8 weeks
Mean change from baseline	KINECT 3	40 mg	6 weeks	AIM-TD	24 mg 36 mg	12 weeks
Mean change from baseline	KINECT 3	80 mg	6 weeks	AIM-TD	24 mg 36 mg	8 weeks
Mean change from baseline	KINECT 3	80 mg	6 weeks	AIM-TD	24 mg 36 mg	12 weeks
Pooled Comparisons						
Mean change from baseline	KINECT 2/3 (pooled)	25-80 mg (pooled)	6 weeks	ARM-TD/AIM-TD (pooled)	12-48 mg (pooled)	6/8 weeks
Mean change from baseline	KINECT 2/3 (pooled)	25-80 mg (pooled)	6 weeks	ARM-TD/AIM-TD (pooled)	24-48 mg (pooled)	6/8 weeks
Response (≥50% improvement)	KINECT 2/3 (pooled)	25-80 mg (pooled)	6 weeks	ARM-TD/AIM-TD (pooled)	12-48 mg (pooled)	12 weeks[a]

[a]Data was not available before end of double-blind treatment (12 weeks).
AIMS, Abnormal Involuntary Movement Scale; ITC, indirect treatment compaison.

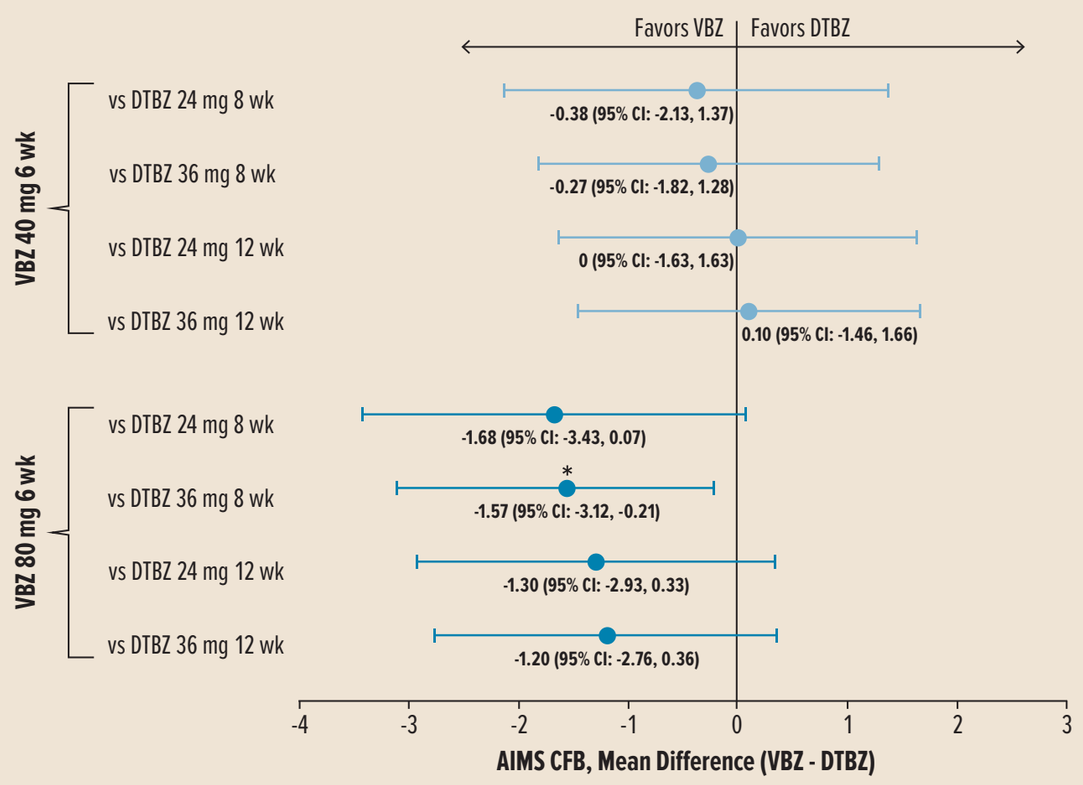
STATISTICAL ANALYSES

- The inverse variance method was used for pooling low and high dosages in the fixed-dose studies (KINECT 3 and AIM-TD) and for estimation of overall AIMS score
- For AIMS ≥50% response, odds ratios (ORs) with 95% confidence intervals (CI) were estimated using the Mantel-Haenszel test; AIMS ≥50% response for ARM-TD was estimated from a figure in a presented poster[7]

RESULTS

- In ITC analysis of AIMS change from baseline by dosage, valbenazine 40 mg at 6 weeks was similar to deutetrabenazine 24 mg and 36 mg at 8 and 12 weeks (**Figure 1**)
- AIMS score change from baseline for valbenazine 80 mg was more favorable than both deutetrabenazine dosages at both time points (8 and 12 weeks) with statistical significance (P<0.05) versus deutetrabenazine 36 mg at 8 weeks

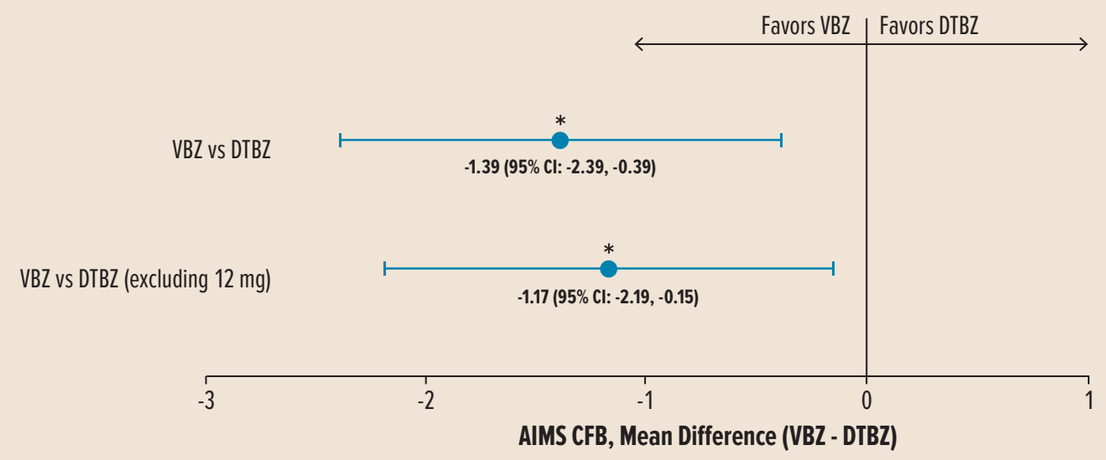
Figure 1. Mean Difference Between Valbenazine and Deutetrabenazine in AIMS CFB



*P<0.05 for VBZ vs DTBZ.
AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; CI, confidence interval; DTBZ, deutetrabenazine; VBZ, valbenazine.

- In the pooled ITC analysis, the AIMS change from baseline for valbenazine at 6 weeks was favorable compared with deutetrabenazine at 6/8 weeks, even in the more conservative analysis in which the 12 mg deutetrabenazine dose was excluded (**Figure 2**)

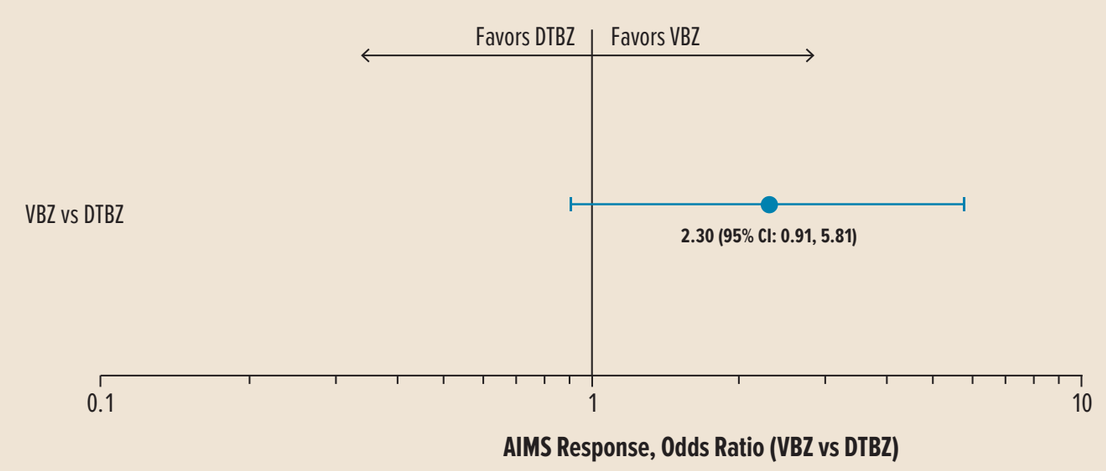
Figure 2. Mean Difference Between Pooled Valbenazine (6 Weeks) and Pooled Deutetrabenazine (6/8 Weeks) in AIMS CFB



*P<0.05 for VBZ vs DTBZ.
AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; CI, confidence interval; DTBZ, deutetrabenazine; VBZ, valbenazine.

- ITC analysis of pooled AIMS response (≥50% total score improvement from baseline) also favored valbenazine as compared with deutetrabenazine (**Figure 3**)

Figure 3. Odds Ratio for Valbenazine (6 Weeks) vs Deutetrabenazine (12 Weeks) for AIMS Response



AIMS, Abnormal Involuntary Movement Scale; CI, confidence interval; DTBZ, deutetrabenazine; VBZ, valbenazine.

CONCLUSIONS

- Both valbenazine and deutetrabenazine were significantly superior to placebo at the end of double-blind treatment in randomized controlled trials; the ITC analysis based on pooled studies and doses indicate that valbenazine at 6 weeks had statistically stronger efficacy in treating TD than deutetrabenazine at 6/8 weeks
- The ITC analyses by dosage groups from KINECT 3 and AIM-TD indicate that the efficacy of valbenazine 80 mg at 6 weeks was generally superior to deutetrabenazine 24 and 36 mg at 8 or 12 weeks, with statistical significance for valbenazine 80 mg (6 weeks) versus deutetrabenazine 36 mg (8 weeks)
- The ITC analyses by dosage groups also indicate that the efficacy of valbenazine 40 mg at 6 weeks was similar to deutetrabenazine 24 mg and 36 mg at 8 or 12 weeks
- Methodological and other study factors such as inclusion criteria, concomitant medications, and TD severity may need to be considered when interpreting the results

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