Effects of Valbenazine on Tardive Dyskinesia After Treatment Withdrawal

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INTRODUCTION

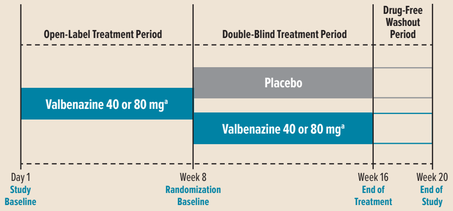
- Tardive dyskinesia (TD) is a persistent and potentially disabling movement disorder associated with prolonged exposure to dopamine receptor blocking agents (e.g., antipsychotics)[1,2]
- Once-daily valbenazine is a highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor approved for the treatment of TD in adults[3]
- Valbenazine was shown to reduce TD symptoms in 3 randomized, double-blind, placebo-controlled trials[4-6] and 3 long-term studies[7-9]
- This phase 4, double-blind, placebo-controlled, withdrawal study (NCT03891862) was conducted to assess the persistence of valbenazine effect in patients with TD

METHODS

STUDY DESIGN

- This study included an initial, 8-week, open-label valbenazine treatment period, followed by an 8-week, randomized, double-blind, placebo-controlled withdrawal period and then a 4-week, no-drug washout period until the final study visit at week 20 (**Figure 1**)
- During the 8-week open-label treatment period, once-daily valbenazine was initiated at 40 mg and escalated to 80 mg after 1 week (dose reduction was allowed for tolerability)
- After 8 weeks of open-label valbenazine, participants were randomized (1:1) to receive 8 weeks of placebo (VBZ/PBO group) or continue taking the same valbenazine dose (VBZ/VBZ group)

Figure 1. Study Design



[a]During the OL treatment period, all participants received 40 mg for 1 week followed by 80 mg for 7 weeks. At any time during the OL or DBPC treatment periods, valbenazine dose reduction to 40 mg was allowed for tolerability. To maintain the blind, subjects receiving placebo continued to receive placebo.
DBPC, double-blind, placebo-controlled; OL, open-label.

PARTICIPANTS

- Key inclusion criteria:
  - Adults aged 18 to 85 years with a clinical diagnosis of schizophrenia/schizoaffective or mood disorder, and neuroleptic-induced TD
  - Moderate or severe TD, qualitatively assessed by an external reviewer at screening
  - Stable psychiatric and medical status
- Key exclusion criteria:
  - Comorbid movement disorder that was more prominent than TD
  - Significant risk for active suicidal ideation or suicidal behavior (Columbia-Suicide Severity Rating Scale [C-SSRS]) or violent behavior
- Stable doses of concomitant medications to treat the psychiatric and medical conditions were allowed

ANALYSES

- Abnormal Involuntary Movement Scale (AIMS) assessments were conducted at study baseline, Week 8 (end of open-label treatment, randomization baseline), Week 12, and Week 16 (end of randomized withdrawal period); patient-reported outcomes were evaluated at study baseline, Week 8, and Week 16
- AIMS total score (sum of items 1-7) was used to assess persistence of effect; based on consensus score by blinded central AIMS video raters
- Patient-reported outcomes included EuroQoL's 5-Dimension 5-Level questionnaire (EQ-5D-5L) and the Sheehan Disability Scale (SDS)
  - The EQ-5D-5L includes a utility index score (range, 0 [health state equivalent to death] to 1 [perfect health]) and a visual analog scale (VAS: range, 0 [worst imaginable health state] to 100 [best imaginable health state])
  - The SDS measures disruption or functional impairment in 3 domains (work/school, social life, and family/home life), with a total sum score (range, 0 [no disruption/impairment] to 30 [extreme disruption/impairment])
- All outcomes were analyzed descriptively; mean values are presented with standard error of the mean (SEM)
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests, vital sign measurements, electrocardiograms (ECGs), and the C-SSRS

RESULTS

- Of 135 participants who enrolled in the study, 118 completed the open-label treatment period and were randomized to receive placebo or valbenazine during the double-blind treatment period
  - Persistence of effect was analyzed in 117 participants with AIMS data available at randomization baseline (VBZ/PBO, n=58; VBZ/VBZ, n=59)
- The majority of participants were male and Hispanic or Latino, and 59% had a primary psychiatric diagnosis of schizophrenia/schizoaffective disorder (**Table 1**)

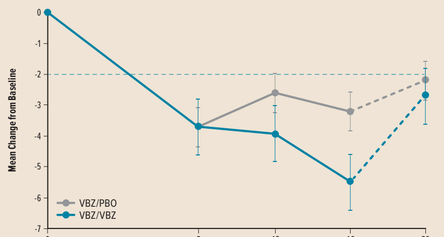
Table 1. Patient Demographics and Baseline Characteristics

	VBZ/PBO n=58	VBZ/VBZ n=59
Age, mean (SD), years	59.2 (8.3)	58.0 (8.0)
Male, n (%)	31 (53.4)	29 (49.2)
Ethnicity, n (%)		
Hispanic or Latino	32 (55.2)	32 (54.2)
Not Hispanic or Latino	26 (44.8)	27 (45.8)
Race, n (%)		
White	36 (62.1)	43 (72.9)
Black	21 (36.2)	16 (27.1)
Multiple	1 (1.7)	0 (0)
BMI, mean (SD), kg/m²	28.4 (5.2)	29.3 (4.8)
Psychiatric diagnosis, n (%)		
Schizophrenia/schizoaffective disorder	36 (62.1)	33 (55.9)
Mood disorder (e.g., MDD, bipolar disorder)	22 (37.9)	26 (44.1)
AIMS total score, mean (SD)	10.3 (3.7)	11.0 (4.1)
BPRS score, mean (SD)[a]	28.2 (6.9)	29.0 (7.2)
C-SSRS lifetime suicidal ideation or behavior, n (%)[a]	23 (39.0)	29 (49.2)

[a]BPRS score and C-SSRS lifetime suicidality are shown for the randomized safety analysis set (VBZ/PBO, n=59; VBZ/VBZ, n=59).
AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; MDD, major depressive disorder; PBO, placebo; SD, standard deviation; VBZ, valbenazine.

- Mean changes in AIMS total score from study baseline to Week 8 (end of open-label period) indicated improvements with valbenazine treatment: VBZ/PBO, -3.7±0.5; VBZ/VBZ, -3.7±0.6 (**Figure 2**)
- Changes from Week 8 (randomization baseline) to Week 16 (end of randomized withdrawal period) indicated initial loss of valbenazine effect after treatment withdrawal: VBZ/PBO, 0.7±0.7; VBZ/VBZ, -1.7±0.4
  - However, mean changes from study baseline to Week 16 suggested some overall persistence of valbenazine effect: VBZ/PBO, -3.2±0.7; VBZ/VBZ, -5.5±0.6

Figure 2. AIMS Total Score Change from Baseline by Visit



VBZ/PBO, n	58	58	56	53	53
VBZ/VBZ, n	59	59	58	56	55

Dashed line indicates minimally clinically important difference (MCID, ≥2 AIMS total score change from study baseline).
AIMS, Abnormal Involuntary Movement Scale; PBO, placebo; VBZ, valbenazine.

- Mean improvements from study baseline to Week 16 for health-related quality of life (EQ-5D-5L) and functional status (SDS) were greater in patients who continued taking valbenazine (**Table 2**)

Table 2. EQ-5D-5L and SDS Scores

		VBZ/PBO				VBZ/VBZ			
		n	Mean (SEM)	n	Mean CFSB (SEM)	n	Mean (SEM)	n	Mean CFSB (SEM)
EQ-5D-5L scores[a]	**Utility index score**								
	Study BL	59	0.71 (0.03)	-	-	59	0.64 (0.04)	-	-
	Week 8 (randomization BL)	59	0.81 (0.02)	59	0.10 (0.03)	59	0.71 (0.03)	59	0.07 (0.03)
	Week 16	53	0.81 (0.03)	53	0.10 (0.03)	56	0.80 (0.03)	56	0.17 (0.04)
	Health state VAS score								
	Study BL	59	74.3 (2.3)	-	-	59	72.9 (2.6)	-	-
	Week 8 (randomization BL)	59	81.3 (2.0)	59	7.0 (2.4)	59	77.7 (2.2)	59	4.8 (3.0)
	Week 16	53	77.8 (2.5)	53	5.2 (2.6)	56	79.6 (2.1)	56	6.4 (3.0)
SDS scores[b]	**Work/school**								
	Study BL	30	3.2 (0.6)	-	-	27	4.4 (0.6)	-	-
	Week 8 (randomization BL)	25	2.2 (0.5)	23	-1.3 (0.4)	23	3.5 (0.6)	20	-1.5 (0.6)
	Week 16	21	1.6 (0.4)	18	-1.7 (0.4)	20	1.8 (0.5)	17	-2.9 (0.6)
	Social life								
	Study BL	59	3.5 (0.3)	-	-	59	5.1 (0.4)	-	-
	Week 8 (randomization BL)	59	2.1 (0.3)	59	-1.4 (0.3)	59	3.0 (0.4)	59	-2.0 (0.4)
	Week 16	53	2.3 (0.3)	53	-1.2 (0.4)	56	2.3 (0.4)	56	-2.7 (0.4)
	Family/home life								
	Study BL	59	2.9 (0.3)	-	-	59	4.3 (0.4)	-	-
	Week 8 (randomization BL)	59	1.8 (0.3)	59	-1.1 (0.3)	59	2.7 (0.3)	59	-1.5 (0.4)
	Week 16	53	1.9 (0.3)	53	-1.0 (0.4)	56	1.9 (0.3)	56	-2.3 (0.4)
	Total score								
	Study BL	30	9.4 (1.3)	-	-	27	13.6 (1.6)	-	-
	Week 8 (randomization BL)	25	6.5 (1.5)	23	-3.9 (1.1)	23	10.6 (1.9)	20	-4.8 (1.8)
	Week 16	21	4.9 (1.3)	18	-5.7 (1.3)	20	4.9 (1.5)	17	-9.1 (1.5)

[a]Utility index score range: 0 (health condition equivalent to death) to 1 (perfect health). VAS score range: 0 (worst possible health) to 100 (best possible health).
[b]SDS total score range: 0 (no disruption) to 30 (extreme disruption).
BL, baseline; CFSB, change from study baseline (beginning of open-label treatment); EQ-5D-5L, EuroQoL's 5-Dimension 5-Level questionnaire; PBO, placebo; SDS, Sheehan Disability Scale; SEM, standard error of the mean; VAS, visual analog scale; VBZ, valbenazine.

- During the open-label valbenazine treatment period, 32.6% of all participants had ≥1 TEAE; 32.2% (VBZ/PBO) and 23.7% (VBZ/VBZ) had ≥1 TEAE during randomized withdrawal (**Table 3**)
  - Urinary tract infection was the only TEAE reported by ≥5% of participants in any treatment group (VBZ/PBO, n=6 [10.2%])
- Two participants had suicidal ideation during double-blind treatment (VBZ/PBO) and 1 participant reported suicidal ideation during open-label treatment and double-blind treatment (VBZ/VBZ); all 3 participants had a lifetime history of suicidality
- There were no clinically important changes in laboratory parameters, vital signs, or ECG parameters

Table 3. Treatment-Emergent Adverse Events

		DBPC Treatment Period	
	OL VBZ Period N=132	VBZ/PBO n=59	VBZ/VBZ n=59
Summary, n (%)			
Any TEAE	43 (32.6)	19 (32.2)	14 (23.7)
Any serious TEAE	3 (2.3)	2 (3.4)	1 (1.7)
Any TEAE leading to discontinuation	4 (3.0)	1 (1.7)	0 (0)
Deaths[a]	1 (0.8)	0 (0)	0 (0)
TEAEs by preferred term, n (%)[b]			
Pain in extremity	5 (3.8)	0 (0)	0 (0)
Somnolence	4 (3.0)	0 (0)	0 (0)
UTI	4 (3.0)	6 (10.2)	0 (0)
Weight increased	2 (1.5)	0 (0)	2 (3.4)
Fall	2 (1.5)	2 (3.4)	0 (0)
Anemia	1 (0.8)	2 (3.4)	1 (1.7)
Suicidal ideation	1 (0.8)	2 (3.4)	1 (1.7)
Blood CPK increased	1 (0.8)	0 (0)	2 (3.4)
Blood glucose increased	0 (0)	0 (0)	2 (3.4)

[a]One subject had a fatal accidental overdose during OL treatment that was judged not related to study drug; this subject was also included in the count for serious TEAEs.
[b]Reported in ≥3% of participants in any treatment group.
CPK, creatine phosphokinase; DBPC, double-blind, placebo-controlled; OL, open-label; PBO, placebo; TEAE, treatment-emergent adverse event; UTI, urinary tract infection; VBZ, valbenazine.

CONCLUSIONS

- Valbenazine effects diminished after treatment withdrawal at the Week 8 randomization timepoint; however, compared to study baseline, there is some persistence of effect in the 8 weeks following withdrawal of valbenazine (VBZ/PBO)
- Overall mean improvements in TD movements, health status/quality of life, and functionality at work/school, social life and family life were greater in patients who continued receiving once-daily valbenazine
- Valbenazine was well tolerated in participants with TD; no new safety signals were identified during the study

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