Effects of Long-Term Valbenazine on Psychiatric Status in Patients with Tardive Dyskinesia and a Primary Mood Disorder

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INTRODUCTION

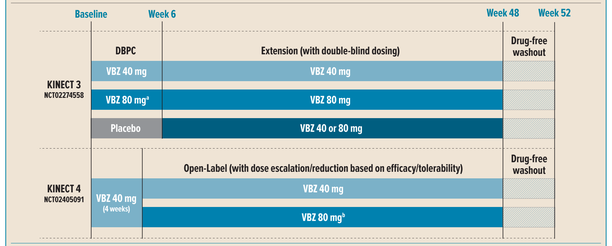
- Valbenazine is approved to treat tardive dyskinesia (TD) in adults based on clinical trials that included patients with mood disorders (e.g., bipolar disorder, major depressive disorder)
- In two long-term phase 3 studies (KINECT 3 [NCT02274558] and KINECT 4 [NCT02405091]),[1,2] sustained TD improvements were observed in participants who received once-daily treatment with valbenazine (40 or 80 mg)
- Pooled data from mood disorder patients in KINECT 3 and KINECT 4 were analyzed post hoc to evaluate changes in TD symptom severity and psychiatric status during long-term valbenazine treatment

METHODS

STUDY DESIGN

- Data were pooled from two long-term phase 3 studies of valbenazine (**Figure 1**), with dose groups pooled as follows:
  - 40 mg: included the 40-mg group from KINECT 3 and participants from KINECT 4 who did not have a dose escalation to 80 mg
  - 80 mg: included the 80-mg group from KINECT 3 and participants from KINECT 4 who were escalated to 80 mg at Week 4
  - Participants who initially received placebo in KINECT 3 were excluded from analyses

Figure 1. Study Design



*Participants who were randomized to 80 mg were initiated at 40 mg for 1 week.
†Includes participants who had a dose reduction to 40 mg due to tolerability issues.
DBPC, double-blind placebo-controlled; VBZ, valbenazine.

PARTICIPANTS

- Key inclusion criteria:
  - Adults aged 18-85 years with a *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) diagnosis of schizophrenia, schizoaffective disorder, or mood disorder and psychiatrically stable (Brief Psychiatric Rating Scale score <50 at screening) prior to study entry
  - DSM-IV diagnosis of neuroleptic-induced TD for ≥3 months prior to screening
  - Moderate or severe TD as qualitatively assessed by an external reviewer at screening
- Key exclusion criteria:
  - Active, clinically significant, and unstable medical condition within 1 month prior to screening
  - Montgomery-Åsberg Depression Rating Scale (MADRS) score >13; Young Mania Rating Scale (YMRS) score >10
  - Comorbid movement disorder that was more prominent than TD
  - Significant risk for active suicidal ideation, suicidal behavior, or violent behavior
- Stable doses of concomitant medications to treat psychiatric and medical disorders were allowed throughout the studies

ANALYSES

- Analyses were conducted in mood disorder participants who received ≥1 dose of valbenazine and had any available post-baseline efficacy assessment
- Changes in TD were assessed at Week 48 (after long-term treatment) and Week 52 (after 4-week washout) using the Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1-7) and Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD)
- AIMS was scored by blinded central video raters (KINECT 3) or site raters (KINECT 4)
- Analyses included: mean change from baseline in AIMS total score, AIMS response (≥50% total score improvement from baseline), CGI-TD mean score, and CGI-TD response (score of 1 ["very much improved"] or 2 ["much improved"])
- Changes in mood symptoms were assessed using YMRS and MADRS total scores and individual item scores
- Data were analyzed descriptively, with no statistical testing between dose groups

RESULTS

- In mood disorder participants, baseline demographics were generally similar between valbenazine dose groups (**Table 1**)
- The majority of participants had bipolar disorder (62.1%); 33.7% had major depression and 4.2% had another mood disorder
- Most participants received concomitant antidepressants (84.2%) and/or antipsychotics (76.8%) during treatment; other common concomitant medications included antiepileptics (47.4%), anxiolytics (38.9%), and anticholinergics (22.1%)
- Mean BPRS, YMRS, and MADRS total scores indicated mood symptom stability at baseline

Table 1. Baseline Characteristics (Mood Disorder Participants)

	Valbenazine 40 mg n=32	Valbenazine 80 mg n=63	All Participants n=95
Age, mean (SD), years	54.9 (9.7)	57.3 (9.6)	56.5 (9.6)
Women, n (%)	20 (62.5)	42 (66.7)	62 (65.3)
White, n (%)	24 (75.0)	48 (76.2)	72 (75.8)
Body mass index, mean (SD), kg/m²	28.3 (5.6)	29.0 (5.5)	28.8 (5.5)
Mood diagnosis, n (%)			
Bipolar disorder	19 (59.4)	40 (63.5)	59 (62.1)
Depression/major depression	12 (37.5)	20 (31.7)	32 (33.7)
Other	1 (3.1)	3 (4.8)	4 (4.2)
Concomitant medications, n (%)			
Antidepressants	27 (84.4)	53 (84.1)	80 (84.2)
Antipsychotics	28 (87.5)	45 (71.4)	73 (76.8)
Antiepileptics	9 (28.1)	36 (57.1)	45 (47.4)
Anxiolytics	18 (56.3)	19 (30.2)	37 (38.9)
Anticholinergics	6 (18.8)	15 (23.8)	21 (22.1)
Age at TD diagnosis, mean (SD), years	49.8 (10.4)	51.0 (11.9)	50.6 (11.4)
Age at mood disorder diagnosis, mean (SD), years	34.3 (15.3)	35.5 (13.3)	35.1 (13.9)
BPRS total score at screening, mean (SD)	26.5 (5.8)	27.0 (6.0)	26.8 (5.9)
MADRS total score, mean (SD)	6.8 (3.6)	5.4 (3.9)	5.9 (3.9)
YMRS total score, mean (SD)	2.9 (2.7)	2.6 (2.7)	2.7 (2.7)
AIMS total score, mean (SD)	11.8 (4.4)	13.4 (4.4)	12.9 (4.4)

AIMS, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; TD, tardive dyskinesia; YMRS, Young Mania Rating Scale.

- Based on AIMS and CGI-TD data, mood disorder participants had meaningful and sustained mean TD improvements with valbenazine at Week 48 (end of treatment), with some return towards baseline levels observed at Week 52 (after 4-week washout) (**Table 2**)

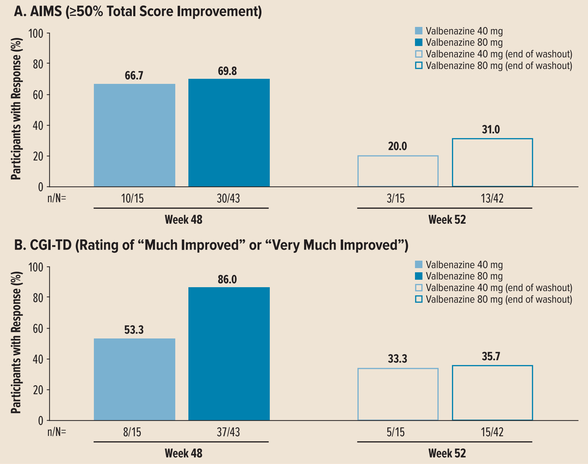
Table 2. Improvements in Tardive Dyskinesia (Mood Disorder Participants)

	Week 48		Week 52	
	Valbenazine 40 mg n=15	Valbenazine 80 mg n=43	Valbenazine 40 mg n=15	Valbenazine 80 mg n=42
AIMS total score, mean change from baseline (SEM)	-7.3 (1.6)	-8.5 (0.9)	-2.1 (1.2)	-3.9 (0.9)
CGI-TD, mean score (SEM)	2.3 (0.3)	1.7 (0.1)	3.3 (0.4)	3.2 (0.3)

AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; SEM, standard error of the mean.

- At Week 48, 69% of all mood disorder participants achieved an AIMS response (≥50% total score improvement) and 77.6% achieved a CGI-TD response (**Figure 2**); the percentage of responders decreased after washout

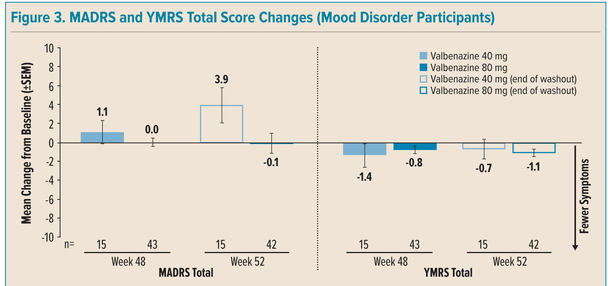
Figure 2. Treatment Response (Mood Disorder Participants)



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia.

- Mood symptoms remained generally stable during the studies, as indicated by minimal changes from baseline in mean total YMRS and MADRS scores (**Figure 3**)

Figure 3. MADRS and YMRS Total Score Changes (Mood Disorder Participants)



MADRS, Montgomery-Åsberg Depression Rating Scale; SEM, standard error of the mean; YMRS, Young Mania Rating Scale.

- Changes in individual items on the MADRS and YMRS scales were <±0.2 in most participants at Weeks 48 and 52, indicating no clinically meaningful changes or worsening in specific mood symptoms or domains (**Table 3**)

Table 3. MADRS and YMRS Item Score Changes (Mood Disorder Participants)

Mean Score Change (SEM)	Week 48		Week 52	
	Valbenazine 40 mg n=15	Valbenazine 80 mg n=43	Valbenazine 40 mg n=15	Valbenazine 80 mg n=42
MADRS items				
Reported sadness	-0.1 (0.2)	0.0 (0.2)	0.1 (0.3)	-0.1 (0.2)
Apparent sadness	0.2 (0.2)	0.1 (0.2)	0.7 (0.3)	-0.0 (0.2)
Inner tension	-0.1 (0.3)	0.1 (0.2)	0.3 (0.2)	-0.0 (0.2)
Reduced sleep	0.5 (0.5)	-0.3 (0.3)	0.4 (0.5)	-0.3 (0.2)
Reduced appetite	0.2 (0.3)	-0.0 (0.1)	0.4 (0.3)	-0.0 (0.1)
Concentration difficulties	0.2 (0.3)	-0.1 (0.2)	0.3 (0.3)	0.0 (0.2)
Lassitude	0.3 (0.3)	0.1 (0.2)	0.8 (0.3)	0.0 (0.2)
Inability to feel	-0.2 (0.2)	0.1 (0.1)	0.5 (0.3)	0.0 (0.1)
Pessimistic thoughts	-0.1 (0.1)	0.2 (0.1)	0.5 (0.3)	0.1 (0.2)
Suicidal thoughts	0.1 (0.1)	0.0 (0.1)	0.0 (0.0)	0.1 (0.1)
YMRS items				
Elevated mood	-0.1 (0.1)	-0.0 (0.1)	-0.1 (0.1)	-0.1 (0.1)
Increased motor activity/energy	-0.2 (0.1)	-0.1 (0.1)	-0.1 (0.2)	-0.0 (0.1)
Sexual interest	0.0 (0.1)	0.0 (0.0)	0.1 (0.2)	-0.0 (0.0)
Sleep	-0.1 (0.2)	-0.3 (0.2)	0.1 (0.3)	-0.3 (0.1)
Irritability	-0.1 (0.2)	0.2 (0.1)	-0.1 (0.3)	0.1 (0.1)
Speech (rate and amount)	-0.3 (0.2)	-0.2 (0.2)	-0.4 (0.2)	-0.2 (0.1)
Language/thought disorder	-0.1 (0.2)	-0.1 (0.1)	-0.1 (0.2)	-0.1 (0.1)
Content	-0.3 (0.2)	-0.3 (0.2)	-0.4 (0.2)	-0.3 (0.2)
Disruptive/aggressive behavior	-0.2 (0.1)	0.0 (0.1)	0.3 (0.4)	-0.0 (0.0)
Appearance	-0.1 (0.1)	0.0 (0.1)	0.1 (0.1)	0.0 (0.1)
Insight	0.1 (0.1)	-0.1 (0.1)	0.0 (0.0)	-0.1 (0.1)

MADRS, Montgomery-Åsberg Depression Rating Scale; SEM, standard error of the mean; YMRS, Young Mania Rating Scale.

- Based on available Columbia-Suicide Severity Rating Scale (C-SSRS) data, most mood disorder participants had no suicidal ideation at baseline (97.9% [93/94])
  - Of these participants, 93.5% (87/93) had no emergence of C-SSRS suicidal ideation at any time during the long-term studies
  - In the 1 participant who had suicidal ideation at baseline ("wish to be dead"), no worsening in C-SSRS score was found at any time during the study

CONCLUSIONS

- As with the overall population, in participants with a mood disorder, long-term treatment with once-daily valbenazine resulted in sustained and clinically meaningful TD improvements
- Mean changes in MADRS and YMRS total scores and item scores indicated that psychiatric symptoms generally remained stable throughout the long-term studies
- Based on the mood symptom stability during the studies, valbenazine did not appear to interfere with the concomitant medications used to maintain psychiatric stability (e.g., antidepressants, antipsychotics); this is consistent with previous studies that indicated a low potential for valbenazine to affect the metabolism or pharmacokinetics of concomitant medications[3]
- Suicidal ideation did not worsen in mood disorder participants who received long-term valbenazine

REFERENCES

1. Factor SA, Remington G, Comella CL, et al. *J Clin Psychiatry*. 2017;78(9):1344-50.
2. Marder SR, Kane JM, Factor SA, et al. *Neuropsychopharmacology*. 2017;43(5):1396-7.
3. Loewen G, Luo R, Smith EB, et al. Presented at the American Society of Clinical Psychopharmacology Meeting, May 29-June 2, 2017.

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