Long-Term Safety and Tolerability of Once-Daily Valbenazine in Patients with Tardive Dyskinesia

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INTRODUCTION

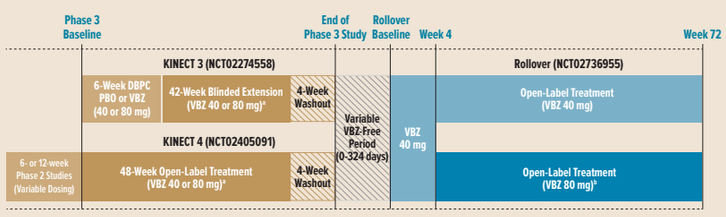
- Tardive dyskinesia (TD) is a persistent and potentially disabling movement disorder associated with prolonged exposure to dopamine receptor blocking agents, such as antipsychotics[1]
- Valbenazine (INGREZZA®) is a novel and highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor that is approved for the treatment of TD in adults
- The long-term safety of valbenazine was demonstrated in two phase 3 studies: KINECT 3 (NCT02274558) and KINECT 4 (NCT02405091)[2,3]; completers from these studies were eligible to participate in a rollover study (NCT02736955) for further treatment
- Data from all 3 studies were analyzed to further evaluate the long-term safety and tolerability of once-daily valbenazine (40 or 80 mg)

METHODS

STUDY DESIGNS AND POOLING

- Three studies were included in this analysis (**Figure 1**)
  - KINECT 3: up to 48 weeks of blinded treatment, followed by 4 weeks of drug-free washout
  - KINECT 4: up to 48 weeks of open-label treatment, followed by 4 weeks of drug-free washout
  - Rollover: up to 72 weeks of open-label treatment, until valbenazine became commercially available
  - Following the 4-week washout of KINECT 3 and KINECT 4, participants who enrolled in the rollover study may have had an additional drug-free period: the mean duration of additional off-drug prior to rollover study start was 66.4 days (range, 0 to 324 days)
- KINECT 3 and KINECT 4 data were pooled, with dose groups defined 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



[a]All KINECT 3 participants randomized to valbenazine in the DBPC period or re-randomized from placebo to valbenazine in the extension period were initiated at 40 mg for 1 week; all KINECT 4 participants were initiated at 40 mg for 4 weeks.
[b]Included participants who had a dose reduction to 40 mg due to tolerability issues.
DBPC, double-blind placebo-controlled; PBO, placebo; VBZ, valbenazine.

PARTICIPANTS

- Key inclusion criteria (KINECT 3 and KINECT 4):
  - *Diagnostic and Statistical Manual of Mental Disorders* (e.g., DSM-IV) diagnosis of schizophrenia, schizoaffective disorder, or mood disorder; required to be psychiatrically stable prior to study entry (e.g., Brief Psychiatric Rating Scale score <50 at screening)
  - 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
- The key inclusion criterion for the rollover study was completion of KINECT 3 or KINECT 4
- Key exclusion criteria (KINECT 3 and KINECT 4):
  - Active, clinically significant, and unstable medical condition within 1 month prior to screening
  - Comorbid movement disorder 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 participants who received ≥1 dose of study drug and had any available post-baseline data
  - Data from KINECT 3 and KINECT 4 were pooled for analysis (pooled long-term population)
  - Data from the rollover study were analyzed separately (rollover population)
- Safety assessments included:
  - Treatment-emergent adverse events (TEAEs)
  - Calgary Depression Scale for Schizophrenia (CDSS) and Positive and Negative Syndrome Scale (PANSS) in participants with schizophrenia/schizoaffective disorder (KINECT 3 and KINECT 4 only)
  - Montgomery-Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) in participants with a mood disorder (KINECT 3 and KINECT 4 only)
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Vital signs and electrocardiograms (ECGs)
- All data were analyzed descriptively, with no statistical testing between valbenazine dose groups

RESULTS

- Within the pooled long-term population and the rollover population, baseline characteristics were generally similar between valbenazine dose groups (**Table 1**)

Table 1. Baseline Characteristics

	Pooled Long-Term Population			Rollover Population		
	40 mg n=107	80 mg[a] n=197	All N=304	40 mg n=35	80 mg n=117	All[b] N=160
Age, mean (SD), years	56.3 (9.3)	57.0 (9.4)	56.8 (9.4)	57.3 (8.9)	57.9 (8.8)	57.9 (8.8)
Male, n (%)	58 (54.2)	104 (52.8)	162 (53.3)	13 (37.1)	63 (53.8)	81 (50.6)
White, n (%)	61 (57.0)	128 (65.0)	189 (62.2)	21 (60.0)	86 (73.5)	111 (69.4)
BMI, mean (SD), kg/m^2	28.5 (5.8)	28.4 (5.5)	28.4 (5.6)	29.2 (5.5)	28.5 (5.5)	28.8 (5.5)
Schizophrenia/schizoaffective disorder, n (%)	75 (70.1)	134 (68.0)	209 (68.8)	23 (65.7)	75 (64.1)	104 (65.0)
BPRS total score at screening, mean (SD)	30.0 (7.3)	28.1 (6.7)	28.7 (7.0)	27.3 (6.3)	26.1 (5.6)	26.6 (6.0)
C-SSRS lifetime suicidality, n (%)	40 (37.4)	83 (42.1)	123 (40.5)	11 (31.4)	46 (39.3)	60 (37.5)
Psychiatric scales scores, mean (SD)[c]						
PANSS total	54.3 (11.5)	49.2 (12.0)	51.0 (12.0)	NA	NA	NA
PANSS positive symptoms	12.6 (3.7)	11.3 (3.9)	11.8 (3.8)	NA	NA	NA
PANSS negative symptoms	14.7 (4.7)	13.3 (5.0)	13.8 (4.9)	NA	NA	NA
PANSS general psychopathology	27.0 (6.2)	24.6 (5.6)	25.5 (5.9)	NA	NA	NA
CDSS total	2.0 (2.3)	1.9 (2.2)	2.0 (2.2)	NA	NA	NA
MADRS total	6.8 (3.6)	5.4 (3.9)	5.9 (3.9)	NA	NA	NA
YMRS total	2.9 (2.7)	2.6 (2.7)	2.7 (2.7)	NA	NA	NA

[a]Included participants who escalated to 80 mg at Week 4 and remained on 80 mg and participants who escalated to 80 mg at Week 4 and had a subsequent dose reduction to 40 mg.
[b]Included 8 participants who had a dose reduction from 80 mg to 40 mg after Week 4.
[c]PANSS and CDSS administered to participants with schizophrenia/schizoaffective disorder; MADRS and YMRS administered to participants with a mood disorder.
BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; C-SSRS, Columbia-Suicide Severity Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; NA, not assessed; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; YMRS, Young Mania Rating Scale.

- In the pooled long-term population, 71.7% of participants had ≥1 TEAE, and 15.5% discontinued due to a TEAE (**Table 2**)
  - Headache and urinary tract infection (8.9% each) were the most commonly reported TEAEs in all participants
- In the rollover population, 9.4% of participants had ≥1 TEAE through Week 4; after Week 4, 49.0% of participants had ≥1 TEAE, and 4.5% discontinued due to a TEAE (**Table 2**)
  - No TEAE was reported in ≥5% of all participants

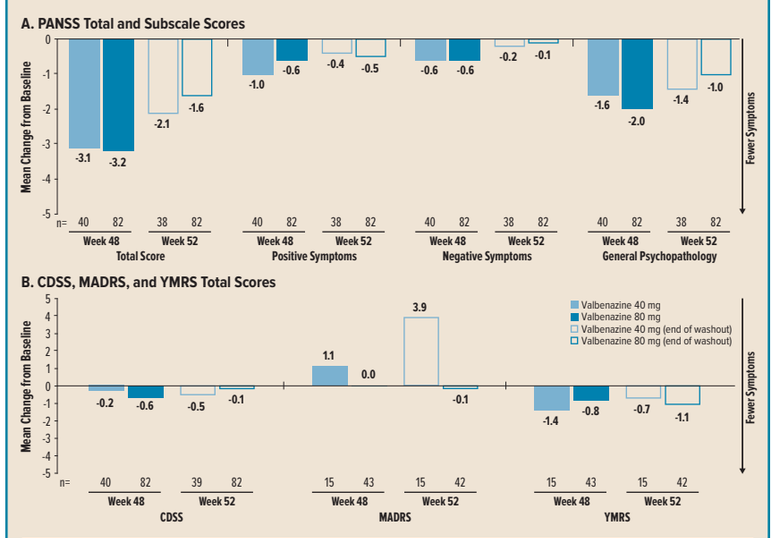
Table 2. Treatment-Emergent Adverse Events

	Pooled Long-Term Population[a]			Rollover Population[b]		
	40 mg n=107	80 mg[c] n=197	All N=304	40 mg n=32	80 mg n=117	All[d] N=157
Summary, n (%)						
Any TEAE	75 (70.1)	143 (72.6)	218 (71.7)	14 (43.8)	56 (47.9)	77 (49.0)
Any serious TEAE	17 (15.9)	34 (17.3)	51 (16.8)	2 (6.3)	10 (8.5)	14 (8.9)
Any TEAE leading to discontinuation	21 (19.6)	26 (13.2)	47 (15.5)	0	6 (5.1)	7 (4.5)
Deaths[e]	0	3 (1.5)	3 (1.0)	0	3 (2.6)	4 (2.5)
TEAEs by preferred term, n (%)[f]						
Headache	11 (10.3)	16 (8.1)	27 (8.9)	1 (3.1)	4 (3.4)	5 (3.2)
Urinary tract infection	10 (9.3)	17 (8.6)	27 (8.9)	1 (3.1)	6 (5.1)	7 (4.5)
Somnolence	11 (10.3)	13 (6.6)	24 (7.9)	0	0	4 (2.5)
Fatigue	12 (11.2)	7 (3.6)	19 (6.3)	0	0	0
Dizziness	5 (4.7)	13 (6.6)	18 (5.9)	1 (3.1)	0	1 (0.6)
Suicidal ideation	8 (7.5)	9 (4.6)	17 (5.6)	1 (3.1)	3 (2.6)	4 (2.5)

[a]At any time during the study; [b]From Week 4 to the end of the study; [c]Included participants who escalated to 80 mg at Week 4 and remained on 80 mg and participants who escalated to 80 mg at Week 4 and had a subsequent dose reduction to 40 mg; [d]Included 8 participants who had a dose reduction from 80 mg to 40 mg after Week 4; [e]All deaths (pooled long-term population: 1 breast cancer, 1 multiple organ failure, 1 sudden death possibly due to cardiovascular event; rollover population: 1 chronic obstructive pulmonary disease exacerbation, 1 septic syndrome, 1 alcohol-induced coma, and 1 hypertensive heart disease) were judged by the study investigators as not related to study drug; [f]Reported in ≥5% of all participants in the long-term pooled population.
TEAE, treatment-emergent adverse event.

- In the pooled long-term population, mean changes from baseline to Week 48 (end of treatment) and Week 52 (end of 4-week washout) in PANSS, CDSS, MADRS, and YMRS scores indicated that psychiatric status generally remained stable in both valbenazine dose groups (**Figure 2**)

Figure 2. Mean Changes from Baseline in Psychiatric Scale Scores (Pooled Long-Term Population)



CDSS, Calgary Depression Scale for Schizophrenia; MADRS, Montgomery-Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.

- Based on available C-SSRS data, almost all participants in the pooled long-term population (97.7% [296/303]) and the rollover population (97.5% [156/160]) had no suicidal ideation at baseline (score=0) (**Table 3**)
  - Most of these participants continued to have no emergence of suicidal ideation at any time during the long-term studies (93.2% [276/296]) or the rollover study (98.1% [153/156])
  - Among participants who had some suicidal ideation at baseline (score=1 to 3: pooled long-term population, n=7; rollover population, n=4), none had a worsening in C-SSRS score at any time during treatment

Table 3. Columbia-Suicide Severity Rating Scale Shifts from Baseline

		Baseline Score	Maximum Suicidal Ideation Score at Any Time During the Study[a]					
			0	1	2	3	4	5
Pooled Long-Term Population	All Participants (n=303)	0	276	8	6	1	2	3
		1	3	3	0	0	0	0
		2	0	0	0	0	0	0
		3	1	0	0	0	0	0
Rollover Population	All Participants (n=160)	0	153	1	2	0	0	0
		1	1	1	0	0	0	0
		2	0	0	1	0	0	0
		3	0	0	0	1	0	0

[a]0=no suicidal ideation, 1=wish to be dead, 2=non-specific active suicidal thoughts, 3=active suicidal ideation with any methods (not plan) without intent to act, 4=active suicidal ideation with some intent to act, 5=active suicidal ideation with specific plan and intent.

- There were no clinically important changes in laboratory parameters, vital signs, or ECG parameters

CONCLUSIONS

- No new safety signals were found in adults with TD who received long-term treatment with valbenazine, including those who received >1 year of treatment during the rollover study
- Psychiatric stability was generally maintained, as indicated by minimal changes in psychiatric scale mean scores
- Few participants experienced any emergence of suicidal ideation during long-term valbenazine treatment; the incidence of suicidal ideation in the long-term pooled population was similar to the incidence with placebo during the 6-week phase of KINECT 3[4]
- These results indicate that once-daily valbenazine may be an appropriate long-term treatment for managing TD in adults

REFERENCES

1. Vijayakumar D, Jankovic J. *Drugs*. 2016;76:779-87.
2. Factor SA, Remington G, Comella CL, et al. *J Clin Psychiatry*. 2017;78:1344-50.
3. Marder SR, Kane JM, Factor SA, et al. *Neuropsychopharmacology*. 2017;43:S396-7.
4. Hauser RA, Factor SA, Marder SR, et al. *Am J Psychiatry*. 2017;174,5:476-84.

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