Long-Term Effects of Valbenazine on Tardive Dyskinesia in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder: Results from an Open-Label, Rollover Study

Dimitri Grigoriadis,[1] Stephen R. Marder,[2] Jean-Pierre Lindenmayer,[3] Cherian Verghese,[4] Joshua Burke,[1] Roland Jimenez,[1] Khodayar Farahmand,[1] Scott Siegert[1]

[1]Neurocrine Biosciences, Inc., San Diego, CA; [2]University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA; [3]New York University School of Medicine, New York, NY; [4]Keystone Clinical Studies, LLC, Norristown, PA

INTRODUCTION

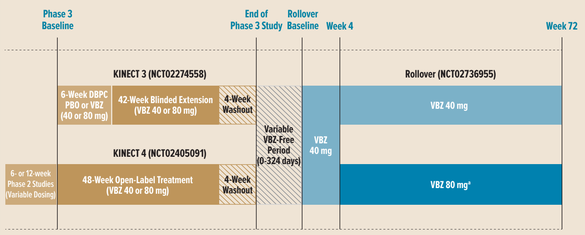
- Tardive dyskinesia (TD) is a persistent and disruptive movement disorder associated with prolonged exposure to antipsychotics and other dopamine receptor blocking agents[1,2]
- Valbenazine (INGREZZA®) is a novel and highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor that is approved for the treatment of TD in adults
- The long-term efficacy and safety of valbenazine was demonstrated in two phase 3 studies (KINECT 3 extension [NCT02274558] and KINECT 4 [NCT02405091])[3,4] in which patients received up to 48 weeks of once-daily valbenazine (40 or 80 mg)
- Completers from KINECT 3 and KINECT 4 were eligible to participate in a rollover study (NCT02736955) for further treatment after a variable valbenazine-free period
- Data from the rollover study were analyzed post hoc to further assess the long-term safety and tolerability of once-daily valbenazine in adults with schizophrenia/schizoaffective disorder or a mood disorder

METHODS

STUDY DESIGN

- The open-label study included patients who completed KINECT 3 or KINECT 4 (48 weeks of valbenazine treatment and 4 weeks of valbenazine-free washout) (**Figure 1**)
  - KINECT 4 included ~50 participants from an earlier phase 2 study
  - All participants restarted once-daily valbenazine at 40 mg for 4 weeks
  - Dosage was escalated to 80 mg at the end of Week 4 based on clinician judgment of safety/tolerability and TD improvement
  - One dose reduction to 40 mg was allowed after Week 4 if 80 mg was not tolerated
  - Participants unable to tolerate 40 mg were discontinued from the study
- Participants received treatment for up to 72 weeks or until valbenazine became commercially available
- Stable doses of concomitant medications to treat psychiatric disorders and comorbid medical conditions were allowed

Figure 1. Study Design



[a]Includes 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:
  - Adults with neuroleptic-induced TD and a *Diagnostic and Statistical Manual of Mental Disorders* (e.g., DSM-IV) psychiatric diagnosis of schizophrenia, schizoaffective disorder, or mood disorder who completed KINECT 3 or KINECT 4
  - Psychiatrically stable prior to study entry (Brief Psychiatric Rating Scale score <50)
- Key exclusion criteria:
  - Active, clinically significant, and unstable medical condition
  - Clinically significant parkinsonism per investigator judgment
  - Significant risk for active suicidal ideation or suicidal behavior (Columbia-Suicide Severity Rating Scale [C-SSRS]) or violent behavior

ANALYSES

- All outcomes were analyzed descriptively in participants who received ≥1 dose of study drug and had ≥1 available post-baseline assessment
- Subgroups were defined by psychiatric diagnosis: schizophrenia/schizoaffective disorder or mood disorder
- Assessments included the Clinical Global Impression of Severity-TD (CGIS-TD: range, 1 "normal, not at all ill" to 7 "extremely ill") and the Patient Satisfaction Questionnaire (PSQ: range, 1 "very satisfied" to 5 "very dissatisfied")
  - Mean CGIS-TD scores were analyzed at every 12-week visit in each diagnosis subgroup
  - Percentages of participants with a CGIS-TD score ≤2 ("normal, not at all ill" or "borderline ill") or PSQ score ≤2 ("very satisfied" or "somewhat satisfied") were also assessed
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests, vital sign measurements, electrocardiograms (ECGs), and the C-SSRS

RESULTS

- Of the 224 participants who completed KINECT 3 or KINECT 4, 161 (71.9%) enrolled in the rollover study (71 from KINECT 3; 90 from KINECT 4); 1 participant without post-baseline data was excluded
  - 138 (85.7%) were ongoing in the study when it was terminated
  - Few reached Week 60 (n=4) and none reached Week 72 because valbenazine became commercially available before reaching those visits
  - Reasons for discontinuation prior to study termination were withdrawal of consent (n=8), adverse events (n=5), death (n=4, not related to treatment), non-compliance (n=3), investigator decision (n=2), and lost to follow-up (n=1)
- There were more participants in the schizophrenia/schizoaffective disorder subgroup (n=104) than in the mood disorder subgroup (n=56)
- Within each diagnosis subgroup, baseline characteristics were generally similar between valbenazine dose groups (**Table 1**)
  - Compared to the schizophrenia/schizoaffective disorder subgroup, the mood subgroup had fewer men, fewer African-American participants, and were older at time of psychiatric diagnosis and TD diagnosis

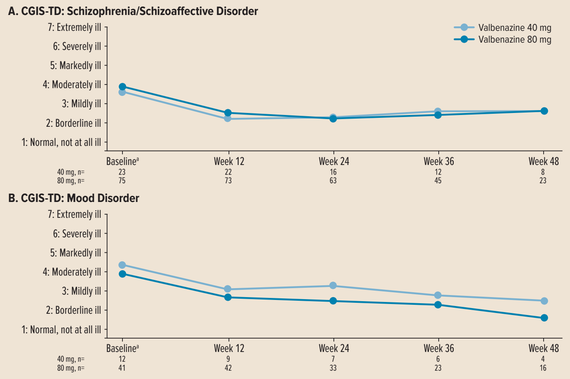
Table 1. Baseline Characteristics by Diagnosis Subgroup

	Schizophrenia/Schizoaffective Disorder			Mood Disorder		
	VBZ 40 mg (n=23)	VBZ 80 mg (n=75)	All[a] (n=104)	VBZ 40 mg (n=12)	VBZ 80 mg (n=42)	All[a] (n=56)
Age, mean (SD), years	55.9 (9.4)	57.9 (9.0)	57.5 (8.9)	59.9 (7.6)	58.0 (8.7)	58.4 (8.6)
Male, n (%)	10 (43.5)	52 (69.3)	66 (63.5)	3 (25.0)	11 (26.2)	15 (26.8)
Race, n (%)						
Caucasian	11 (47.8)	49 (65.3)	62 (59.6)	10 (83.3)	37 (88.1)	49 (87.5)
African-American	12 (52.2)	26 (34.7)	41 (39.4)	2 (16.7)	4 (9.5)	6 (10.7)
BMI, mean (SD), kg/m²	29.6 (6.0)	28.6 (5.8)	28.9 (5.8)	28.2 (4.6)	28.5 (5.0)	28.6 (4.9)
Age at diagnosis, mean (SD), years						
Psychiatric diagnosis	27.1 (8.3)	28.7 (11.4)	28.2 (10.6)	36.0 (12.0)	33.9 (13.3)	34.7 (13.2)
Tardive dyskinesia	46.3 (11.5)	46.3 (9.1)	45.8 (9.7)	51.8 (10.3)	52.1 (9.4)	52.2 (9.7)
BPRS total score at screening, mean (SD)	29.0 (6.1)	26.7 (5.7)	27.4 (6.1)	24.0 (5.5)	25.0 (5.2)	25.0 (5.6)
C-SSRS lifetime history at screening, n (%)						
Suicidal ideation	6 (26.1)	21 (28.0)	29 (27.9)	4 (33.3)	15 (35.7)	20 (35.7)
Suicidal behavior	5 (21.7)	21 (28.0)	27 (26.0)	5 (41.7)	11 (26.2)	17 (30.4)

[a]Includes participants who had a dose reduction from 80 to 40 mg after Week 4.
BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; SD, standard deviation; VBZ, valbenazine.

- CGIS-TD mean scores indicated sustained global improvements with valbenazine (40 and 80 mg) in both diagnosis subgroups (**Figure 2**)

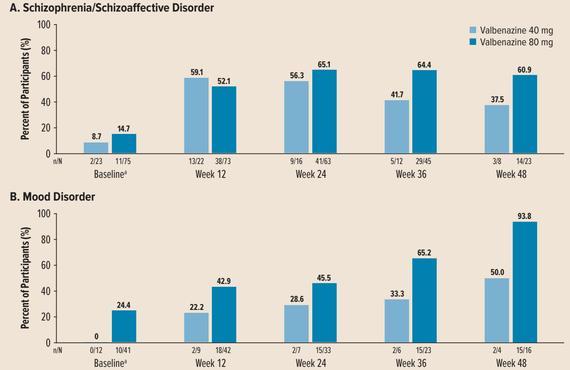
Figure 2. Global TD Improvements by Diagnosis Subgroup (Clinician-Rated)



[a]Baseline of rollover study (after variable valbenazine-free period of 0-324 days).
Data not shown for participants who had a dose reduction from 80 mg to 40 mg (schizophrenia/schizoaffective disorder, n=6; mood disorder, n=2).
CGIS-TD, Clinical Global Impression of Severity-Tardive Dyskinesia.

- In both diagnosis subgroups, the percentage of participants with a CGIS-TD score ≤2 increased from baseline (prior to restarting valbenazine) to Week 48 (**Figure 3**)

Figure 3. Meaningful TD Response (CGIS-TD Score ≤2) by Diagnosis Subgroup (Clinician-Rated)



[a]Baseline of rollover study (after variable valbenazine-free period of 0-324 days).
Data not shown for participants who had a dose reduction from 80 mg to 40 mg (schizophrenia/schizoaffective disorder, n=6; mood disorder, n=2).
CGIS-TD, Clinical Global Impression of Severity-Tardive Dyskinesia.

- At baseline, 99.0% (103/104) of all schizophrenia/schizoaffective disorder participants and 98.2% (55/56) of all mood disorder participants were "very satisfied" or "somewhat satisfied" with their prior valbenazine experience (PSQ score ≤2)
  - At Week 48, high levels of satisfaction with valbenazine were reported in the schizophrenia/schizoaffective disorder subgroup (97.1% [33/34]) and the mood disorder subgroup (100% [22/22])
- During treatment initiation (40 mg for 4 weeks), 6.7% of all schizophrenia/schizoaffective disorder participants and 14.3% of all mood disorder participants had any TEAE; discontinuation due to TEAE was reported in none of the schizophrenia/schizoaffective disorder participants and 3.6% of all mood disorder participants
- From Week 4 to the end of study, the incidence of any TEAE in all valbenazine-treated patients was similar between diagnosis subgroups (**Table 2**)
  - Less than 7% of all participants in either subgroup discontinued due to TEAEs

Table 2. Treatment-Emergent Adverse Events (Week 4 to the End of Study)

	Schizophrenia/Schizoaffective Disorder			Mood Disorder		
	VBZ 40 mg (n=22)	VBZ 80 mg (n=75)	All[a] (n=103)	VBZ 40 mg (n=10)	VBZ 80 mg (n=42)	All[a] (n=54)
Summary, n (%)						
Any TEAE	9 (40.9)	36 (48.0)	50 (48.5)	5 (50.0)	20 (47.6)	27 (50.0)
Any serious TEAE	2 (9.1)	9 (12.0)	13 (12.6)	0	1 (2.4)	1 (1.9)
Any TEAE leading to discontinuation	0	6 (8.0)	7 (6.8)	0	0	0
Deaths[b]	0	3 (4.0)	4 (3.9)	0	0	0
TEAEs by preferred term, n (%)[c]						
Urinary tract infection	1 (4.5)	1 (1.3)	2 (1.9)	0	5 (11.9)	5 (9.3)
Back pain	1 (4.5)	3 (4.0)	4 (3.9)	1 (10.0)	2 (4.8)	3 (5.6)
Tremor	0	1 (1.3)	2 (1.9)	0	2 (4.8)	3 (5.6)
Cough	0	2 (2.7)	2 (1.9)	1 (10.0)	1 (2.4)	3 (5.6)
Suicidal ideation	0	1 (1.3)	1 (1.0)	1 (10.0)	2 (4.8)	3 (5.6)

[a]Includes participants with a dose reduction from 80 to 40 mg after Week 4.
[b]Deaths occurred due to chronic obstructive pulmonary disease, sepsis syndrome, alcohol-induced coma, and hypertensive heart disease; none were judged as related to treatment.
[c]Reported in ≥5% of all participants in either diagnosis subgroup.
40 mg: never had a dose increase to 80 mg; 80 mg: received 40 mg and increased to 80 mg, without a subsequent dose reduction.
TEAE, treatment-emergent adverse event; VBZ, valbenazine.

- Based on available C-SSRS data, almost all schizophrenia/schizoaffective disorder participants (99.0% [103/104]) and mood disorder participants (94.6% [53/56]) 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 rollover study (schizophrenia/schizoaffective disorder: 99.0% [102/103]; mood disorder: 96.2% [51/53])
  - Among participants who had some suicidal ideation at baseline (score=1 to 3), none had any worsening in C-SSRS score at any time during treatment

Table 3. C-SSRS Shifts from Baseline by Diagnosis Subgroup

		Maximum Suicidal Ideation Score at Any Time During the Study[a]					
	Baseline Score	0	1	2	3	4	5
Schizophrenia/Schizoaffective Disorder (n=104)	0	102	0	1	0	0	0
	1	0	1	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
Mood Disorder (n=56)	0	51	1	1	0	0	0
	1	1	0	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, without specific plan, 5=active suicidal ideation with specific plan and intent.
C-SSRS, Columbia-Suicide Severity Rating Scale.

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

CONCLUSIONS

- Clinician-based assessments indicated ongoing and meaningful TD improvements in participants who received >1 year of treatment with once-daily valbenazine (40 or 80 mg)
- Patient satisfaction rates with valbenazine remained high throughout the rollover study
- Similar results were found in participants with schizophrenia/schizoaffective disorder and those with a mood disorder
- Valbenazine was generally well tolerated and no new safety signals were observed
- Valbenazine may be an appropriate long-term treatment for managing TD in adults with schizophrenia/schizoaffective disorder or a mood disorder

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