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KINECT 3: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Valbenazine (NBI-98854) for Tardive Dyskinesia

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ABSTRACT

Introduction: Tardive dyskinesia (TD) is a persistent and often disabling movement disorder resulting from chronic antipsychotic exposure. There are currently no FDA-approved treatments for TD. Valbenazine (VBZ), a novel, highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor, is designated an FDA breakthrough investigational therapy. VBZ demonstrated favorable efficacy and safety profiles in Phase 1 and 2 studies. The efficacy, safety and tolerability of VBZ for TD were evaluated in a Phase 3 trial (KINECT 3; NCT02274558).

Methods: KINECT 3 was a double-blind, parallel-group, 6-week, placebo-controlled trial in subjects with moderate or severe antipsychotic-induced TD and underlying schizophrenia, schizoaffective disorder, or mood disorder. Subjects were randomized 1:1:1 to placebo: VBZ 40 mg: VBZ 80 mg, taken once-daily. The primary outcome was an intent to treat (ITT) analysis of change from baseline on the Abnormal Involuntary Movement Scale (AIMS) score, assessed by blinded central video raters, for the VBZ 80 mg dose vs. placebo. Safety assessments included adverse event (AE) rates, laboratory, ECG, and psychiatric assessments, including the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), Calgary Depression Scale for Schizophrenia (CDSS), and the Columbia Suicide Severity Rating Scale (C-SSRS).

Results: Sixty-four sites randomized 234 subjects. Sixty-six percent of subjects had schizophrenia or schizoaffective disorder, and 86% were receiving concomitant antipsychotic medications (16% typical, 77% atypical). The mean baseline AIMS score (SD) was 10.1 (4.0). VBZ 80 mg resulted in a significant improvement in AIMS score vs. placebo (LS mean change from baseline -3.2 vs. -0.1; P<0.0001). The AIMS score was also reduced in the VBZ 40 mg group vs. placebo (LS mean change from baseline -1.9 vs. -0.1; *P*=0.0021; full description of supportive analyses to be presented). AE rates were similar among all groups and were consistent with prior studies; the most commonly reported AE was somnolence (VBZ 80 mg: 5%, VBZ 40 mg: 4%, placebo: 4%). Three percent of subjects discontinued due to treatment-emergent AEs (VBZ 80 mg: 4%, VBZ 40 mg: 3%, placebo: 3%). Across multiple scales (PANSS, YMRS, MADRS, CDSS, C-SSRS), results were generally similar between VBZ and placebo, and psychiatric status was stable.

Conclusion: Once-daily administration of VBZ was associated with a significant improvement in TD and was generally well tolerated in subjects with underlying schizophrenia, schizoaffective disorder or mood disorder (e.g., bipolar disorder and major depressive disorder). Both VBZ doses were generally well tolerated, even when taken with a wide range of concomitant medications, including antipsychotic agents. Psychiatric scales indicated no apparent increased risk in psychiatric symptoms, depression or suicidality with VBZ during the trial. VBZ may be a promising therapy for TD.

INTRODUCTION

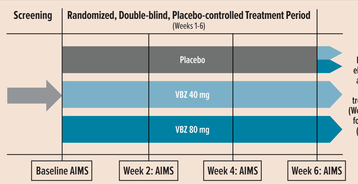
- Tardive dyskinesia (TD) is a movement disorder that may occur in patients exposed to dopamine receptor blocking agents (DRBAs), such as antipsychotics[1]
- There are currently no FDA-approved medications indicated for the treatment of TD[1]
- The vesicular monoamine transporter 2 (VMAT2) is a presynaptic protein that regulates monoamine uptake (e.g., dopamine) from the cytoplasm to the synaptic vesicle for storage and release[2]
- VMAT2 inhibition modulates dopaminergic transmission, potentially reducing synaptic dopamine levels and improving TD symptoms
- Valbenazine (NBI-98854), a novel, highly selective inhibitor of VMAT2, is in Phase 3 development for the treatment of TD
- Valbenazine has a favorable PK profile, allowing once-daily dosing with no required titration
- In an earlier Phase 2 trial (KINECT 2; NCT01733121),[3] once-daily valbenazine demonstrated a favorable efficacy and safety profile in the treatment of TD
- A Phase 3 trial (KINECT 3; NCT02274558) was conducted to evaluate the efficacy, safety and tolerability of 2 doses of valbenazine (40 and 80 mg) administered once daily in adults with TD

METHODS

STUDY DESIGN

- KINECT 3 was a randomized, double-blind, parallel-group, fixed-dose study (**Figure 1**)
- Findings from the 6-week, placebo-controlled, treatment period are presented
- Subjects were randomized (1:1:1) to placebo, valbenazine 40 mg, or valbenazine 80 mg once daily

Figure 1. Study Design



At the Week 6 visit, subjects initially randomized to placebo were re-randomized to VBZ 40 mg or 80 mg. Subjects initially randomized to VBZ 40 mg or 80 mg remained at their current dose. Subjects initially randomized or re-randomized to VBZ 80 mg received 40 mg for the first week.
AIMS, Abnormal Involuntary Movement Scale; VBZ, valbenazine.

SUBJECTS

- Key inclusion criteria:
  - DSM-IV diagnosis of antipsychotic-induced TD for ≥3 months prior to screening
  - Moderate or severe TD, as indicated by item 8 (severity of abnormal movement overall) of the Abnormal Involuntary Movement Scale (AIMS); rated by a blinded, external reviewer using a video of the subject's AIMS assessment at screening
  - DSM-IV diagnosis of schizophrenia or schizoaffective disorder or mood disorder (stable per investigator) and Brief Psychiatric Rating Scale score <50 at screening
- Key exclusion criteria:
  - Active, clinically significant, and unstable medical condition within 1 month prior to screening
  - Comorbid movement disorder (e.g., parkinsonism, akathisia, truncal dystonia) that is more prominent than TD
  - Significant risk for active suicidal ideation, suicidal behavior, or violent behavior

EFFICACY PARAMETERS

- Analyzed in the intent-to-treat (ITT) population, defined as all subjects from the Safety population (defined below) who also had baseline and ≥1 post-baseline AIMS assessments
- Fixed-sequence testing procedure to control for family-wise error rate and multiplicity:
  - [1] Primary endpoint: change from baseline to Week 6 in AIMS dyskinesia total score (i.e., sum of AIMS items 1-7) for valbenazine 80 mg vs. placebo
  - [2] Key secondary endpoint: Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) mean score at Week 6 for valbenazine 80 mg vs. placebo
  - [3] AIMS score change from baseline to Week 6 for valbenazine 40 mg vs. placebo
  - [4] CGI-TD score at Week 6 for valbenazine 40 mg vs. placebo
  - For any test result in this sequence to be considered statistically significant, all previous results in the list were required to have met the 0.05 level of significance
- Differences between valbenazine (80 or 40 mg) and placebo were analyzed using a mixed-effects model for repeated measures (MMRM)
- Effect size was estimated using the Cohen's *d* calculation

SAFETY PARAMETERS

- Analyzed descriptively in the Safety population, defined as all subjects who were randomized to a treatment group and dispensed study drug
- Assessments: adverse events (AEs), physical exam, vital signs, electrocardiogram (ECG), laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Abnormal movement scales: Barnes Akathisia Rating Scale (BARS) and Simpson-Angus Scale (SAS)
- Psychiatric status scales: Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Young Mania Rating Scale (YMRS), and Montgomery-Asberg Depression Rating Scale (MADRS)

RESULTS

SUBJECTS

- Of the 234 randomized patients, 205 (87.6%) completed the 6-week placebo-controlled treatment period
- Demographics were similar across treatment groups (**Table 1**)

Table 1. Baseline Characteristics (ITT Population)

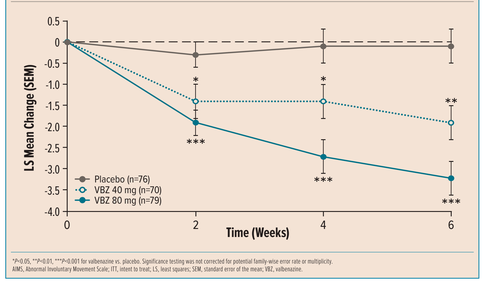
	Placebo n=76	VBZ 40 mg n=70	VBZ 80 mg n=79
Age, mean years (SD)	57 (10.5)	55 (8.6)	56 (10.1)
Male, n (%)	42 (55.3)	40 (57.1)	39 (49.4)
Schizophrenia/schizoaffective disorder, n (%)	50 (65.8)	46 (65.7)	52 (65.8)
BPRS score at screening, mean (SD)	29.3 (7.0)	30.2 (7.4)	29.1 (6.6)
AIMS score, mean (SD)	9.9 (4.3)	9.8 (4.1)	10.4 (3.6)
Psychiatric Scale Scores, mean (SD)[a]			
PANSS Positive Symptoms score[b]	12.9 (3.3)	12.8 (3.7)	13.0 (4.2)
PANSS Negative Symptoms score[b]	15.4 (4.5)	14.9 (4.7)	14.3 (3.9)
PANSS General Psychopathology score[b]	27.5 (5.3)	27.2 (6.5)	26.8 (5.5)
CDSS score[b]	2.0 (2.2)	2.0 (2.1)	1.9 (2.2)
YMRS score[c]	1.8 (2.3)	3.0 (3.0)	3.3 (3.2)
MADRS score[c]	5.2 (2.9)	7.1 (3.8)	5.4 (4.0)

[a]In the Safety population; [b]placebo n=50, VBZ 40 mg=48, VBZ 80 mg=52; [c]placebo n=26, VBZ 40 mg=24, VBZ 80 mg=27.
AIMS, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; ITT, intent to treat; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; VBZ, valbenazine; YMRS, Young Mania Rating Scale.

EFFICACY

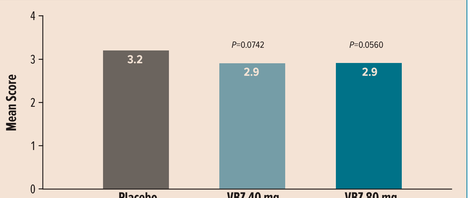
- The primary efficacy parameter was met in this study
  - AIMS score (least squares [LS] mean change from baseline to Week 6, MMRM): valbenazine 80 mg, -3.2; placebo, -0.1; *P*<0.001; effect size, *d*=0.90
  - The remaining steps of the fixed-sequence testing procedure were not met, but a trend towards improvement was observed in the CGI-TD (80 mg, *P*=0.0560; 40 mg, *P*=0.0742; **Figure 3**), as well as for the valbenazine 40 mg AIMS score LS mean change from baseline to Week 6 (-1.9 vs. -0.1 placebo; *P*<0.05)
- For the AIMS score change by study visit, a statistically significant difference between valbenazine (80 and 40 mg) vs. placebo was detected at Weeks 2, 4, and 6 (ITT; **Figure 2**)

Figure 2. AIMS Score LS Mean Change from Baseline through Week 6 (ITT Population)



*P<0.05, **P<0.01, ***P<0.001 for valbenazine vs. placebo. Significance testing was not corrected for potential family-wise error rate or multiplicity.
AIMS, Abnormal Involuntary Movement Scale; ITT, intent to treat; LS, least squares; SEM, standard error of the mean; VBZ, valbenazine.

Figure 3. CGI-TD Mean Score at Week 6 (ITT Population)



CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; ITT, intent to treat; VBZ, valbenazine.

- Psychiatric status remained stable during the study, as indicated by LS mean change from baseline to Week 6 in PANSS, CDSS, YMRS, and MADRS scores (**Table 2**)

Table 2. Psychiatric Scale Scores Change from Baseline to Week 6 (Safety Population)

Psychiatric Scale Scores, LS mean (SEM)	Placebo	VBZ 40 mg	VBZ 80 mg
PANSS Positive Symptoms score[a]	-0.0 (0.5)	-0.5 (0.3)	-0.3 (0.3)
PANSS Negative Symptoms score[a]	-0.0 (0.5)	-0.0 (0.4)	0.5 (0.4)
PANSS General Psychopathology score[a]	-0.2 (0.8)	-1.3 (0.8)	-0.8 (0.5)
CDSS score[a]	-0.1 (0.3)	-0.5 (0.3)	-0.4 (0.3)
YMRS score[b]	0.1 (0.5)	-0.3 (0.5)	-1.1 (0.5)
MADRS score[b]	1.0 (0.9)	0.5 (1.1)	-1.7 (0.9)

[a]placebo n=50, VBZ 40 mg=48, VBZ 80 mg=52; [b]placebo n=26, VBZ 40 mg=24, VBZ 80 mg=27.
CDSS, Calgary Depression Scale for Schizophrenia; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean; VBZ, valbenazine; YMRS, Young Mania Rating Scale.

SAFETY

- A summary of AEs are presented in **Table 3**
  - Treatment-emergent AEs of potential clinical interest (e.g., fatigue, weight increase, blood glucose increase, tremor, depression, anxiety) generally occurred in <3% of subjects treated with valbenazine and at an incidence comparable to (or lower than) placebo

Table 3. Adverse Events (Safety Population)

	Placebo n=76	VBZ 40 mg n=72	VBZ 80 mg n=79
Summary of AEs, n (%)			
Any serious AE	3 (3.9)	4 (5.6)	6 (7.6)
Discontinuation due to AE	2 (2.6)	2 (2.8)	3 (3.8)
Any TEAE	34 (44.7)	28 (38.9)	39 (49.4)
TEAEs by Preferred Term, n (%)[a]			
Somnolence	3 (3.9)	3 (4.2)	4 (5.1)
Akathisia	1 (1.3)	3 (4.2)	2 (2.5)
Arthralgia	1 (1.3)	1 (1.4)	3 (3.8)
Dry mouth	1 (1.3)	4 (5.6)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	3 (3.8)
Dyskinesia	0 (0.0)	0 (0.0)	3 (3.8)
Urinary tract infection	3 (3.9)	3 (4.2)	0 (0.0)

[a]Reported in ≥3% of subjects in either valbenazine group at an incidence greater than placebo.
AE, adverse event; TEAE, treatment-emergent adverse event; VBZ, valbenazine.

- No safety signal was detected for suicidality based on treatment-emergent AEs or C-SSRS responses
- Laboratory parameters were similar across treatment groups; no clinically relevant changes identified
- No notable ECG changes (e.g., QTc prolongation) were found
- No evidence of treatment-emergent parkinsonism or akathisia, or other abnormal movements based on BARS and SAS scores
- Although >85% of subjects were receiving at least 1 concomitant antipsychotic medication (typical, 16%; atypical, 77%), there was no clinical evidence of drug interaction toxicities

CONCLUSIONS

- Once-daily administration of valbenazine 80 mg was associated with a significant improvement in tardive dyskinesia vs. placebo in subjects with schizophrenia, schizoaffective disorder, or mood disorder
- Both valbenazine doses (40 and 80 mg) were generally well tolerated, even though patients were taking a wide range of concomitant medications, including antipsychotic agents
- Results of this study support findings from the earlier Phase 2 study; both trials indicate that valbenazine may be a promising therapy for tardive dyskinesia

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