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Clinical Development of INGREZZA® (valbenazine) Capsules and INGREZZA® SPRINKLE (valbenazine) Capsules in Patients with Tardive Dyskinesia

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the use of INGREZZA and INGREZZA SPRINKLE for the treatment of tardive dyskinesia (TD).

INGREZZA and INGREZZA SPRINKLE are vesicular monoamine transporter 2 (VMAT2) inhibitors indicated for the treatment of adults with TD.[1]

An extensive clinical development program has been conducted to investigate valbenazine (VBZ) including two Phase II studies (KINECT® 1 and 2), two Phase III studies (KINECT® 3 and 4), and one Phase IIIb rollover study (1506). The purpose of this summary document is to respond to your request for a brief summary of the published literature.

Summary of Key Outcomes

KINECT 1: Phase II Study

KINECT 1 was a 12 week (6 week double-blind, 6 week open-label), randomized, double-blind, placebo–controlled (DBPC) Phase II study investigating the safety and efficacy of valbenazine for the treatment of TD. Changes in Abnormal Involuntary Movement Scale (AIMS) scores as rated by onsite investigators for valbenazine and placebo (PBO) at Week 6 were –3.3 and –2.5 (not significant). In a post hoc analysis of AIMS as rated by blinded central video raters, the scores for valbenazine and PBO were –3.3 and –1.5 (p=0.03). Treatment-emergent adverse events (TEAEs) were reported by 41% of participants with 8 discontinuations due to adverse events (AEs; none were reported as related to study drug).

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KINECT 2: Phase II Study

KINECT 2 was a 6 week, randomized, DBPC Phase II study investigating the safety and efficacy of valbenazine (25, 50, or 75 mg) for the treatment of TD. The mean change from baseline in AIMS scores (assessed by blinded central video raters) for valbenazine vs PBO at Week 6 was statistically significant (least squares mean, –2.6 vs –0.2; p=0.0005). No treatment-related serious AEs were reported. The most commonly reported AEs were fatigue (VBZ, 9.8%; PBO, 4.1%) and headache (VBZ, 9.8%; PBO, 4.1%).

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KINECT 3: Phase III Fixed-Dose Study

KINECT 3 was a 6 week, randomized, DBPC Phase III study to assess the efficacy, safety, and tolerability of valbenazine in the treatment of TD. Participants were randomized (1:1:1) to receive PBO, valbenazine 40 mg, or valbenazine 80 mg once daily. The mean change from baseline in AIMS scores (assessed by blinded central video raters) for valbenazine (80 mg/d) vs PBO was statistically significant after 6 weeks of DB treatment (–3.2 vs –0.1; p<0.001). No treatment-related serious AEs were reported. The most commonly reported AEs were dry mouth (VBZ, 0%–6.9%; PBO, 1.3%) and somnolence (VBZ, 5.1%–5.6%; PBO, 3.9%).

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KINECT 3: Phase III Double-Blind Valbenazine Extension Period

Participants who completed the DBPC period in KINECT 3 continued to an extension period of 42 weeks of DB treatment with valbenazine and a 4-week drug-free follow-up. Throughout the valbenazine treatment period (40 or 80 mg/d for 48 weeks), there were sustained reductions from baseline in AIMS total score for valbenazine. The mean AIMS score changes (as assessed by blinded central video raters) at Week 48 were –3.0 for 40 mg and –4.8 for 80 mg. A return toward baseline levels was observed after treatment discontinuation. The most common AEs were diarrhea, headache, urinary tract infection, and dizziness (reported by 3.1%–7.9% of participants).

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KINECT 4: Phase III, Open-Label, Long-Term Study

KINECT 4 was an open-label, long-term study investigating the safety and tolerability of valbenazine (40 or 80 mg/day) in adults with TD. The study included 48 weeks of open-label treatment and a 4-week drug-free follow-up period. During 48 weeks of open-label valbenazine treatment (40 or 80 mg/d), there were sustained reductions in AIMS total scores from baseline during treatment (mean changes at Week 48 as rated by site investigators, –10.2 for 40 mg; –11.0 for 80 mg). A return toward baseline levels was observed after treatment discontinuation. TEAEs were reported by 64.7% of all participants.

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KINECT 1: Phase II Study[2]

Study Design

KINECT 1 was a randomized, double-blind, placebo-controlled (DBPC) Phase II study that investigated the safety and efficacy of valbenazine for the treatment of tardive dyskinesia (TD). The study included 12 weeks of treatment (6 weeks double-blind, 6 weeks open-label) and 4 weeks of follow-up (**Appendix Figure 1**).

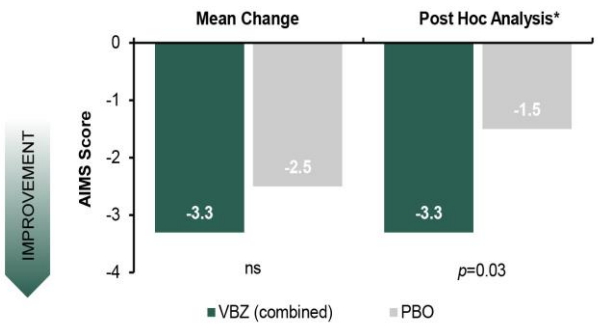
Efficacy

The mean change from baseline in the Abnormal Involuntary Movement Scale (AIMS) total score was used to evaluate change in TD severity, with a decreased AIMS total score from baseline indicating improvement in TD. The AIMS was initially administered by independent site raters who were not involved in the participants' care. Each AIMS assessment was video recorded during the trial according to standardized guidelines. In a post-hoc analysis, AIMS videos were reviewed and scored by consensus by two central video raters who were blinded to study visit and treatment assignment.

Mean AIMS score changes from baseline at Week 6 (primary endpoint) are shown in **Figure 1**.

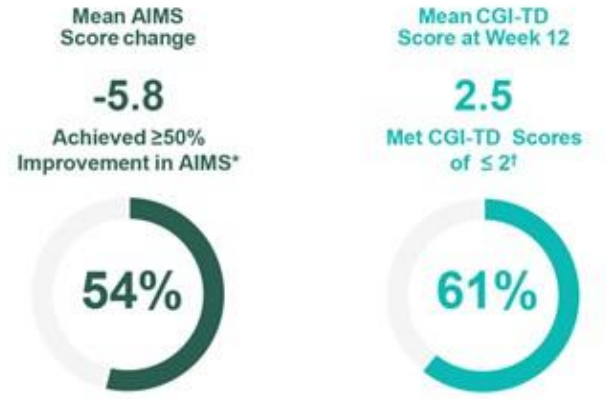
AIMS and Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) scores and responder rates at Week 12 are shown in **Figure 2**. CGI-TD scores range from 1 (very much improved) to 7 (very much worse).

Figure 1. Mean Change in AIMS Score at Week 6 (DB Treatment Period)



AIMS, Abnormal Involuntary Movement Scale; DB, double-blind; ns, not significant; PBO, placebo; VBZ, valbenazine.
*AIMS rated by blinded central video raters.

Figure 2. AIMS and CGI-TD Response Threshold Rates From Baseline to Week 12



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change–Tardive Dyskinesia.
*Defined as ≥50% reduction in AIMS score.
†Defined as score of 1 (very much improved) or 2 (much improved)

Safety

Information on treatment-emergent adverse events (TEAEs) is shown in **Table 1**. Eight participants discontinued the trial due to a TEAE (PBO, n=1; valbenazine 100 mg, n=1; valbenazine 50 mg, n=6), none of which were reported as study-drug related. No clinically relevant changes were observed in laboratory and electrocardiogram (ECG) values, and there were no safety signals in select psychiatric status monitoring scales.

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Table 1. TEAEs Reported at Completion of Open-Label Extension Study (End of Week 16)

Event, n (%)	VBZ 50 mg (n=102)
Overall	42 (41%)
Urinary tract infection	6 (5.9%)
Diarrhea	3 (2.9%)
Fall	3 (2.9%)
Fatigue	3 (2.9%)
Increased appetite	3 (2.9%)
Somnolence	3 (2.9%)

TEAE, treatment-emergent adverse event; VBZ, valbenazine.

KINECT 2: Phase II Study[3]

Study Design

KINECT 2 was a randomized DBPC Phase II study that investigated the safety and efficacy of valbenazine (25, 50, or 75 mg) for the treatment of TD. The study included 6 weeks of double-blind (DB) treatment and 2 weeks of follow-up (**Appendix Figure 2**).

Key Baseline Characteristics

Baseline characteristics were generally similar between the placebo (PBO) and valbenazine groups (**Table 2**).

Table 2. Baseline Characteristics

	PBO (n=49)	VBZ (n=51)
Age, mean (SD), years	55.6 (9.8)	56.7 (10.8)
Male, n (%)	27 (55.1)	30 (58.8)
Mean AIMS score (SD)	7.9 (4.5)	8 (3.5)
Disease category, n (%)		
Schizophrenia/schizoaffective disorder	30 (61.2)	28 (54.9)
Concomitant medications, n (%)[a]		
Antipsychotics	33 (75)	32 (71.1)

AIMS, Abnormal Involuntary Movement Scale; PBO, placebo; VBZ, valbenazine.
[a]Data are for the intent-to-treat population, n=44 placebo, n=45 valbenazine.

Efficacy

The mean change from baseline in the AIMS total score was used to evaluate change in TD severity, with a decreased AIMS total score from baseline indicating improvement in TD. The primary efficacy endpoint was AIMS change from baseline at Week 6 as scored by consensus of two central video raters who were blinded to study visit and treatment assignment.

The mean change in AIMS score at Week 6 and the CGI-TD and Patient Global Impression of Change (PGIC) scores (secondary endpoints) were significantly different (improved) for valbenazine vs PBO groups (**Figure 3**). The PGIC scale, rated on a scale from 1 (very much improved) to 7 (very much worse), was scored by each participant based on their perception of change in TD since baseline.

Figure 3. LS Mean Changes for AIMS, CGI-TD, and PGIC Scores at Week 6

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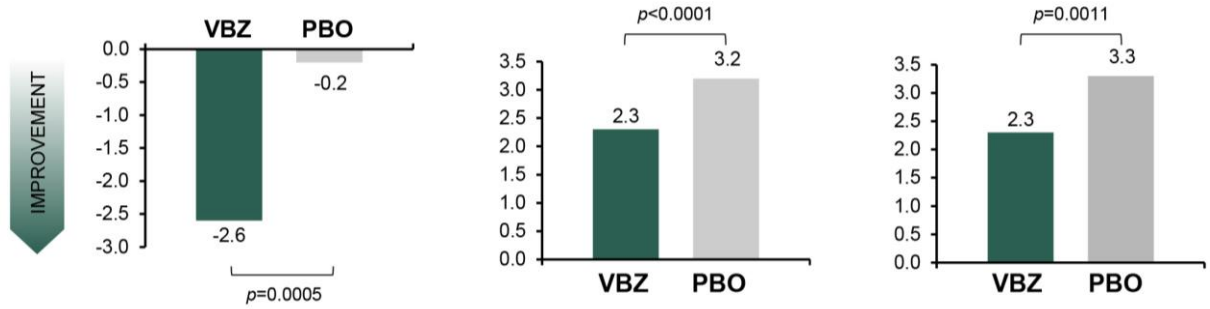
A. AIMS Score (Primary Efficacy Endpoint)

B. CGI-TD* Score (Secondary Efficacy Endpoint)

C. PGIC* Score (Secondary Efficacy Endpoint)



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change–Tardive Dyskinesia; LS, least squares; PGIC, Patient Global Impression of Change; PBO, placebo; VBZ, valbenazine.
*Rated on a scale from 1 (very much improved) to 7 (very much worse).

There were more AIMS, CGI-TD, and PGIC responders in the valbenazine group vs PBO (**Figure 4**).

Figure 4. Response Threshold Rates for Valbenazine vs PBO

A. Participants With ≥50% Improvement in AIMS*

B. CGI-TD Scores of ≤2†

C. PGIC Scores of ≤2†

AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change–Tardive Dyskinesia; PGIC, Patient Global Impression of Change; PBO, placebo; VBZ, valbenazine.
*AIMS response defined as ≥50% score reduction from baseline
†CGI-TD or PGIC response defined as a rating of 1 (very much improved) or 2 (much improved)

Safety

Rates of most commonly reported adverse events (AEs) are summarized in **Table 3**. There were no treatment-related serious AEs and no safety signals triggered from clinical hematology, chemistry, or ECG readings.

Table 3. Most Commonly Reported AEs (n=100)*

Event, n (%)	PBO (n=49)	VBZ (n=51)
Fatigue	2 (4.1)	5 (9.8)
Headache	2 (4.1)	5 (9.8)
Decreased appetite	0	4 (7.8)
Nausea	2 (4.1)	3 (5.9)
Somnolence	1 (2.0)	3 (5.9)
Dry mouth	0	3 (5.9)
Vomiting	0	3 (5.9)
Constipation	3 (6.1)	2 (3.9)
Urinary tract infection	3 (6.1)	2 (3.9)
Sedation	1 (2.0)	2 (3.9)
Back pain	0	2 (3.9)
Dizziness	2 (4.1)	0

AE, adverse event; PBO, placebo; VBZ, valbenazine.
*AEs reported by ≥2 participants.

KINECT 3: Phase III Fixed-Dose Study[4]

Study Design

KINECT 3 was a randomized, DBPC Phase III study to assess the efficacy, safety, and tolerability of valbenazine in the treatment of TD (**Appendix Figure 3**). Participants (n=234) were randomized (1:1:1) to receive PBO, valbenazine 40 mg, or valbenazine 80 mg once daily for 6 weeks.

Participants

Demographics were similar across treatment groups (**Table 4**). Of the 234 randomized participants, 205 completed the 6-week PBO-controlled treatment period.

Table 4. Baseline Characteristics (ITT Population)

	PBO (n=76)	VBZ 40 mg (n=72)	VBZ 80 mg (n=79)
Age, mean (SD) years	57 (10.5)	55 (8.5)	56 (10.1)
Male, n (%)	42 (55.3)	42 (58.3)	39 (49.4)
Schizophrenia/schizoaffective disorder, n (%)	50 (65.8)	48 (66.7)	52 (65.8)
Mean (SD) AIMS score	9.9 (4.3)	9.7 (4.1)	10.4 (3.6)
Concomitant medications, n (%)			
Antipsychotics	63 (82.9)	66 (91.7)	65 (82.3)
Anticholinergics	22 (28.9)	30 (41.7)	32 (40.5)

AIMS, Abnormal Involuntary Movement Scale; ITT, intent-to-treat; PBO, placebo; VBZ, valbenazine.

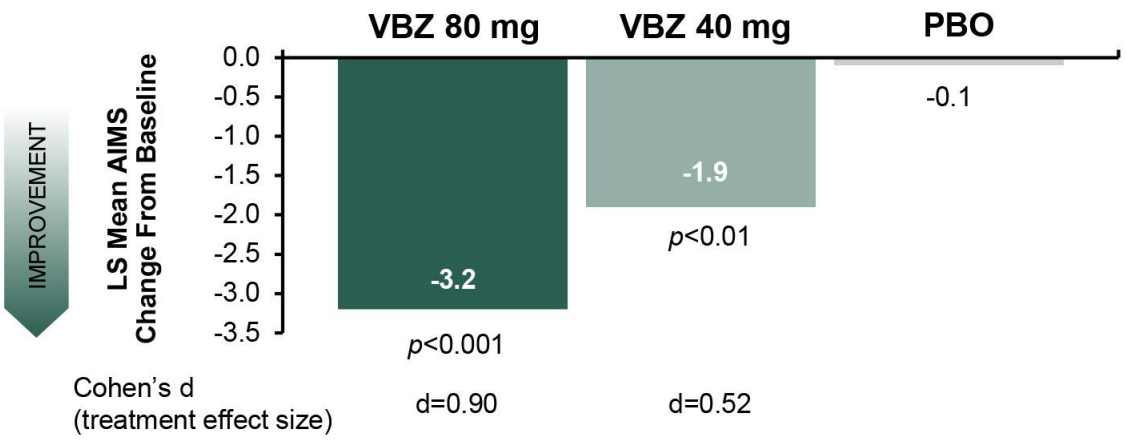
Efficacy

The mean change from baseline in the AIMS total score was used to evaluate change in TD severity, with a decreased AIMS total score from baseline indicating improvement in TD. The primary efficacy endpoint was AIMS change from baseline at Week 6 as scored by consensus of two central video raters who were blinded to study visit and treatment assignment.

The least squares mean AIMS score change from baseline at the end of Week 6 for valbenazine 80 mg vs PBO (primary efficacy endpoint) was statistically significant (**Figure 5** and **Figure 6A**). Mean change in CGI-TD for valbenazine 80 mg vs PBO (key secondary efficacy endpoint) did not reach statistical significance in the intent-to-treat (ITT) group (p=0.0560; **Figure 6B**).

AIMS and CGI-TD data from supportive analyses of the valbenazine 40-mg ITT group and per-protocol data sets are also reported in **Figures 6A and 6B**. The least squares mean AIMS score changes from baseline were statistically different for valbenazine (80 and 40 mg) vs PBO at all study visits (Weeks 2, 4, and 6; data not shown).

Figure 5. Mean Changes in AIMS Score at Week 6 for 40 mg and 80 mg* Valbenazine vs PBO

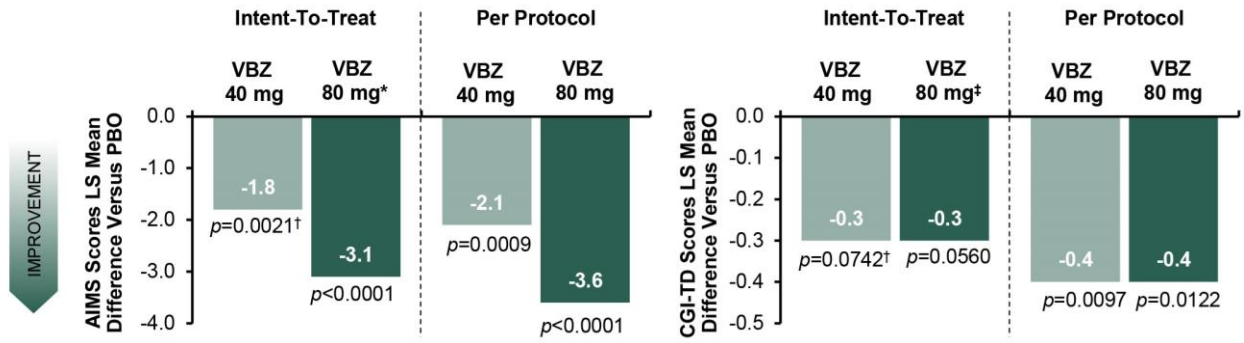


AIMS, Abnormal Involuntary Movement Scale; LS, least squares; PBO, placebo; VBZ, valbenazine.
*Primary endpoint.

Figure 6. AIMS and CGI-TD Score Differences From PBO at Week 6

A. AIMS

B. CGI-TD



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change–Tardive Dyskinesia; LS, least squares; PBO, placebo; VBZ, valbenazine.
*Primary efficacy endpoint.
†Assessment of statistical significance of *p*-values precluded based on prespecified, fixed-sequence testing procedure.
‡Key secondary efficacy endpoint.
Intent-to-treat group included all participants in the safety population who had ≥1 postbaseline AIMS assessment, The per-protocol data set excluded participants without detectable VBZ plasma concentrations and was prespecified for supportive analyses.

Safety

Rates of most commonly reported AEs are summarized in **Table 5**. There were no treatment-related serious AEs and no safety signals observed from clinical hematology, chemistry, or ECG readings.

Table 5. Most Commonly Reported AEs in the Safety Population (n=227)

Event, n (%)	PBO (n=76)	VBZ 40 mg (n=72)	VBZ 80 mg (n=79)
Any event	33 (43.4)	29 (40.3)	40 (50.6)
Events by preferred term			
Somnolence	3 (3.9)	4 (5.6)	4 (5.1)
Akathisia	1 (1.3)	3 (4.2)	2 (2.5)
Dry mouth	1 (1.3)	5 (6.9)	0
Suicidal ideation	4 (5.3)	3 (4.2)	1 (1.3)
Arthralgia	1 (1.3)	1 (1.4)	3 (3.8)
Headache	2 (2.6)	2 (2.8)	2 (2.5)
Vomiting	0	0	3 (3.8)
Dyskinesia	0	0	3 (3.8)
Anxiety	0	1 (1.4)	2 (2.5)
Insomnia	1 (1.3)	1 (1.4)	2 (2.5)
Fatigue	1 (1.3)	2 (2.8)	1 (1.3)
Urinary tract infection	3 (3.9)	3 (4.2)	0
Weight increase	0	1 (1.4)	2 (2.5)

AE, adverse event; PBO, placebo; VBZ, valbenazine.

KINECT 3: Phase III Double-Blind Valbenazine Extension Period[5]

Study Design

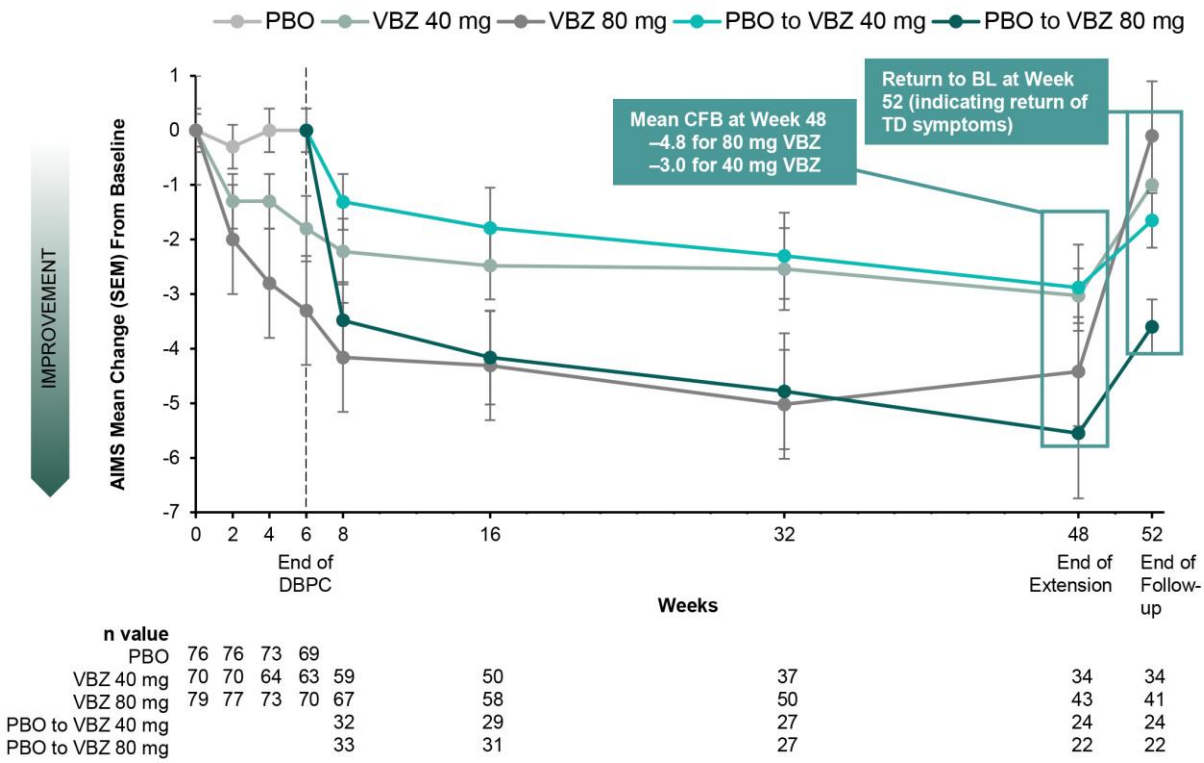
Participants who completed the DBPC period in the KINECT 3: Phase III fixed-dose study continued to an extension period, which consisted of 42 weeks of DB treatment with valbenazine and a 4-week drug-free follow-up (**Appendix Figure 4**). All participants received valbenazine during the extension study treatment period. Those who received valbenazine during the DBPC period continued at the same dose. Those who received PBO during the DBPC period were re-randomized to treatment with valbenazine 80 or 40 mg/day.

Efficacy

The mean change from baseline in the AIMS total score was used to evaluate change in TD severity, with a decreased AIMS total score from baseline indicating improvement in TD. As in the DBPC period, all AIMS scoring during the double-blind extension was based on the consensus of two central AIMS video raters who were blinded to study visit and treatment dose.

Throughout treatment, there were sustained reductions from baseline in AIMS total score for the 40 mg and 80 mg valbenazine dose groups (**Figure 7**). After treatment discontinuation, a return toward baseline levels was observed.

Figure 7. Mean Change in AIMS Score From Baseline (ITT Population)



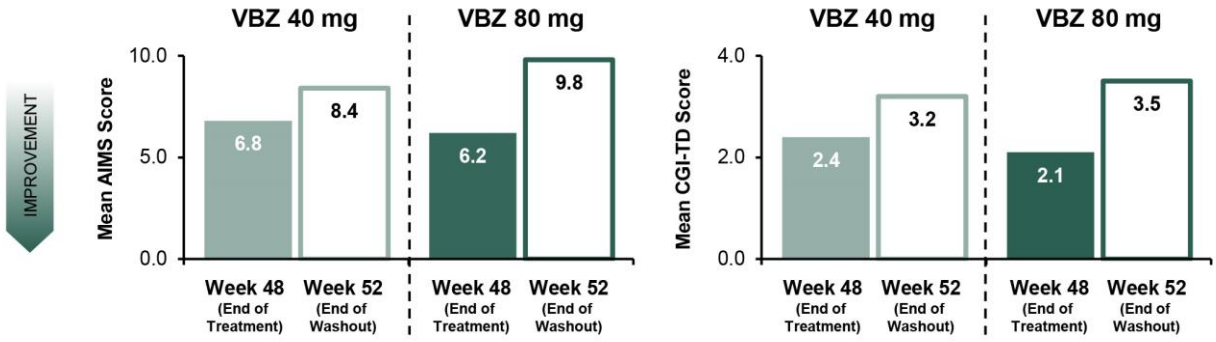
AIMS, Abnormal Involuntary Movement Scale; BL, baseline; CFB, change from baseline; DBPC, double-blind, placebo-controlled; ITT, intent-to-treat; PBO, placebo; SEM, standard error of the mean; VBZ, valbenazine.
AIMS scoring was based on the consensus of 2 blinded, central video raters. After Week 6, subjects initially receiving PBO were re-randomized to receive VBZ 40 or 80 mg until the end of Week 48. Error bars represent ±1 SEM.

Mean AIMS and CGI-TD scores at Weeks 48 and 52 are shown in **Figure 8**. The higher scores at Week 52 suggest TD symptoms were returning toward baseline levels following discontinuation of valbenazine.

Figure 8. Mean AIMS and CGI-TD Scores at Weeks 48 and 52

A. AIMS Score

B. CGI-TD Score



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change–Tardive Dyskinesia; VBZ, valbenazine.
CGI-TD rated on a scale of 1 (very much improved) to 7 (very much worse).

Safety

During the extension period (post–Week 6 to Week 48), 69.2% of participants had ≥1 TEAE. Rates of commonly reported TEAEs are summarized in **Table 6**. There were no clinically important changes in clinical laboratory, vital signs, or ECG parameters during the extension treatment or washout periods.

Table 6. TEAE

Event, n (%)	VBZ 40 mg (n=97)	VBZ 80 mg (n=101)
Any event	60 (61.9)	77 (76.2)
Events by preferred term*		
Headache	7 (7.2)	7 (6.9)
Urinary tract infection	6 (6.2)	7 (6.9)
Diarrhea	3 (3.1)	8 (7.9)
Dizziness	4 (4.1)	7 (6.9)
Suicidal ideation	5 (5.2)	5 (5.0)
Depression	6 (6.2)	2 (2.0)

TEAE, treatment-emergent adverse event; VBZ, valbenazine.
*TEAEs reported by ≥5% of participants.

KINECT 4: Phase III, Open-Label, Long-Term Study[6,7]

Study Design

KINECT 4 was an open-label, long-term study that investigated the safety and tolerability of valbenazine (40 or 80 mg/day) in adults with TD. The study included 48 weeks of open-label treatment and a 4-week drug-free follow-up period (**Appendix Figure 5**).

Participants

Baseline characteristics were similar across treatment groups. AIMS scores for treatment groups are shown in **Table 7**.

Table 7. AIMS Scores* at Baseline

	VBZ 40 mg (n=45)	VBZ 80 mg† (n=107)	All Participants‡ (n=163)
Mean (SD) AIMS score*	10.2 (3.9)	10.0 (3.9)	10.0 (3.8)
Schizophrenia/schizoaffective disorder, n (%)	37 (82.2)	76 (71.0)	119 (73.0)
Concomitant medications, n (%)			
Antipsychotics	40 (88.9)	95 (88.8)	144 (88.3)
Anticholinergics	10 (22.2)	33 (30.8)	44 (27.0)

AIMS, Abnormal Involuntary Movement Scale; VBZ, valbenazine.
*Assessed by central video raters.
†Received VBZ 40 mg/d for 4 weeks before escalation to 80 mg/d.
‡Includes 11 participants who had a dose reduction from 80 mg/day to 40 mg/day after Week 4.

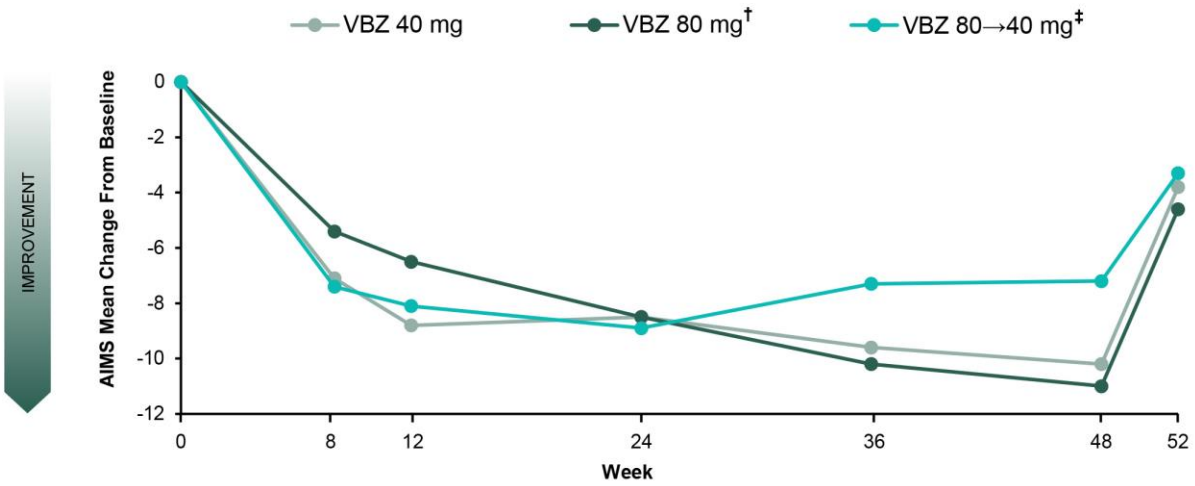
Efficacy

The mean change from baseline in the AIMS total score was used to evaluate change in TD severity, with a decreased AIMS total score from baseline indicating improvement in TD. Mean changes from baseline in AIMS was scored by site raters (at baseline and weeks 8, 12, 24, 36, 48, and 52) and by consensus of two blinded, central video raters at limited visits (baseline, Week 8 [first visit after dose escalation], and Week 52 [after washout]). The central video raters were blinded study visit and treatment assignment. The CGI-TD was scored by site raters.

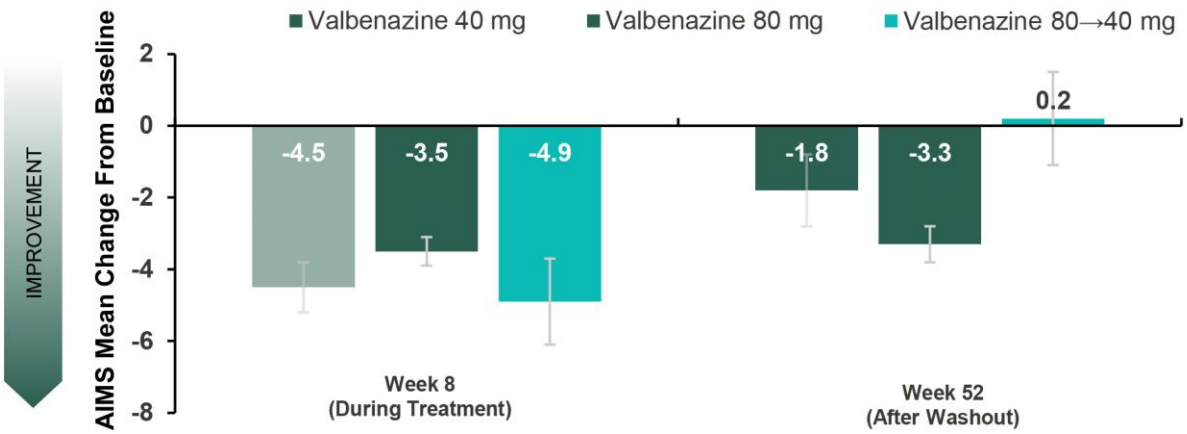
There were sustained reductions in AIMS total scores from baseline during treatment and a return toward baseline levels of dyskinesia after treatment withdrawal (**Figure 9**).

Figure 9. Mean Changes From Baseline in AIMS Score

A. Site Raters§



B. Central Video Raters*



AIMS, Abnormal Involuntary Movement Scale; VBZ, valbenazine.
§AIMS total scores were assessed by site investigators at baseline, Weeks 8, 12, 24, 36, 48, and 52.
†Received VBZ 40 mg/d for 4 weeks before escalation to 80 mg/d.
‡Received escalated 80-mg/d dose, which was subsequently decreased to 40 mg/d due to tolerability.
*AIMS total scores were assessed by blinded central video raters at baseline, Weeks 8 and 52.

For all dose groups, CGI-TD and PGIC mean scores (as reported by clinicians and participants) improved during Weeks 8 to 48, with some loss of effect at Week 52 (data not shown). The response threshold rates of CGI-TD or PGIC response (defined as a score of 1 ["very much improved"] or 2 ["much improved"]) also generally increased from Weeks 8 to 48, followed by a decrease at Week 52 (data not shown). CGI-TD and PGIC response rates at Week 48 in the valbenazine 80 mg/day group are shown in **Figure 10**.

Figure 10. CGI-TD and PGIC Response Threshold Rates* With 80 mg valbenazine at Week 48

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CGI-TD, Clinical Global Impression of Change–Tardive Dyskinesia; VBZ, valbenazine.
*Defined as a CGI-TD or PGIC score of 1 (very much improved) or 2 (much improved).

Safety

Rates of TEAEs during the study are shown in **Table 8**. There was 1 death due to breast cancer, which was determined not to be related to study drug. Change from baseline in vital signs, ECG parameters, and laboratory test values were generally small and not clinically significant.

Table 8. TEAE (Total* and Most Common†)

Event, n (%)	All Participants* (n=153)
Any event	99 (64.7)
Events by preferred term†	
Urinary tract infection	13 (8.5)
Headache	8 (5.2)

TEAE, treatment-emergent adverse event; VBZ, valbenazine.
*Occurring any time during valbenazine treatment.
†Reported in ≥5% of all participants from Week 4 to end of study.

1506: Phase IIIb, Long-Term, Open-Label Rollover Study[8]

Study Design

Study 1506 was an open-label, rollover phase IIIb study that enrolled participants who completed KINECT 3 or KINECT 4 (**Appendix Figure 6**). Participants in 1506 received valbenazine treatment (40 or 80 mg/day) for up to 72 weeks or until valbenazine became commercially available. At study termination, 85.7% (138/161) of participants were still active in the study; 4 participants reached Week 60, and none reached Week 72.

Participants

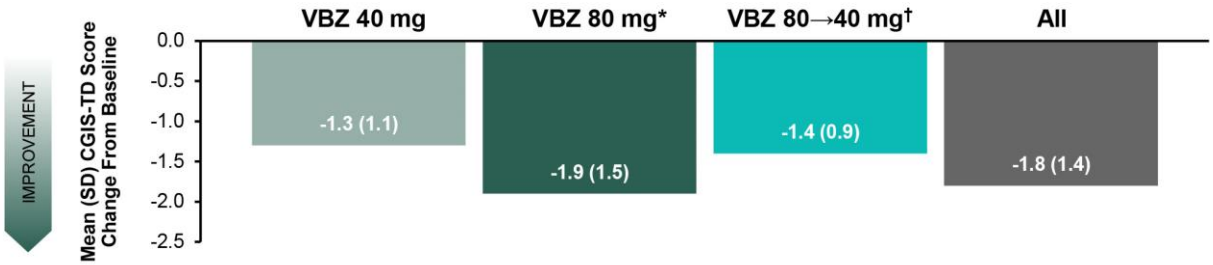
Baseline characteristics were generally similar across treatment groups. At baseline (before re-initiation of valbenazine treatment), Clinical Global Impression of Severity–Tardive Dyskinesia (CGIS-TD) mean (SD) score was 3.9 (1.2) in all participants.

Mean (SD) total duration of valbenazine exposure was 19.7 (3.4) months (range, 9.9-26.9 months).

Efficacy

Mean CGIS-TD score changes from baseline are shown in **Figure 11**.

Figure 11. Mean (SD) CGIS-TD Score Changes From Baseline to Week 48



CGIS-TD, Clinical Global Impression of Severity–Tardive Dyskinesia; VBZ, valbenazine.
CGIS-TD rated on a scale of 1 (normal, not at all ill) to 7 (among the most extremely ill patients).
*Received VBZ 40 mg/d for 4 weeks before escalation to 80 mg/d.
†Received escalated 80-mg/d dose, which was subsequently decreased to 40 mg/d due to tolerability.

The percent of participants with CGIS-TD scores ≤2 (normal/not ill or borderline ill) increased from baseline to Week 48 (**Figure 12**).

Figure 12. Percentage of Participants With a CGIS-TD Score ≤2*

CGIS-TD, Clinical Global Impression of Severity–Tardive Dyskinesia.
*Defined as a CGIS-TD score of 1 (normal, not at all ill) or 2 (borderline ill).

Satisfaction with prior and current valbenazine treatment was assessed using the Patient Satisfaction Questionnaire (PSQ). PSQ rated on a scale of 1 (very satisfied) to 5 (very dissatisfied). The percentage of all participants with a PSQ score ≤2 was high at baseline and remained high throughout the study (**Figure 13**).

Figure 13. Mean PSQ Scores and Percentage of Participants Reporting a PSQ Score ≤2*

PSQ, Patient Satisfaction Questionnaire; VBZ, valbenazine.
*Defined as a PSQ score of 1 "very satisfied" or 2 "somewhat satisfied".
†Baseline rating is participant rating of prior VBZ experience.

Safety

Incidence of TEAEs before and after Week 4 (dose escalation) are shown in **Table 9**. No TEAE occurred in ≥5% of participants during the study (before or after Week 4), and no single TEAE was reported in >2% of participants before dose escalation at Week 4.

Table 9. TEAE Rates Before and After Week 4*

	Baseline to Week 4†	Week 4 to End of Study
Event, n (%)	**VBZ 40 mg (n=160)**	**All Participants‡ (n=157)**
Any event	15 (9.4)	77 (49)
Events by preferred term†		
Urinary tract infection	0	7 (4.5)
Back pain	1 (0.6)	7 (4.5)

TEAE, treatment-emergent adverse event; VBZ, valbenazine.
*All participants received VBZ 40 mg/d for 4 weeks. At Week 4, dosing could be escalated to 80 mg/d based on tolerability and clinical assessment of tardive dyskinesia.
†No single TEAE was reported by >2% of participants before Week 4.
‡Reported in ≥2% of all participants from Week 4 to end of study.

This letter and the enclosed material are provided in response to your unsolicited medical information inquiry. Please feel free to contact Neurocrine Medical Information at (877) 641-3461 or medinfo@neurocrine.com if you would like to request additional information.

References

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Jimenez R, et al. Kinect Extension: 12-week Treatment of Tardive Dyskinesia with NBI-98854. Poster presented at 18th International Congress of Parkinson's Disease and Movement Disorders; June 8–12, 2014; Stockholm, Sweden.
3. O'Brien CF, et al. NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *Mov Disord*. 2015 Oct;30(12):1681-7.
4. Hauser RA, et al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry*. 2017;174:5,476-484.
5. Factor SA, et al. The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. *J Clin Psychiatry*. 2017 Nov/Dec;78(9):1344-1350.
6. Marder SR, et al. A phase 3, 1-year, open-label trial of valbenazine in adults with tardive dyskinesia. *J Clin Psychopharmacol*. 2019 Nov/Dec;39(6):620-627.
7. Marder, SR, et al. KINECT 4: A Phase 3, One-Year, Open-Label Trial of Valbenazine in Participants With Tardive Dyskinesia. Poster presented at the 2017 American College of Neuropsychopharmacology Annual Congress, Palm Springs, CA.
8. Lindenmayer JP, et al. A long-term, open-label study of valbenazine for tardive dyskinesia. *CNS Spectrums*. 2020:1-9.

Enclosure:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. INGREZZA [Important Safety Information]. San Diego, CA: Neurocrine Biosciences, Inc.
C. Jimenez R, et al. Kinect Extension: 12-week Treatment of Tardive Dyskinesia with NBI-98854. Poster presented at 18th International Congress of Parkinson's Disease and Movement Disorders; June 8–12, 2014; Stockholm, Sweden.
D. Marder, SR, et al. KINECT 4: A Phase 3, One-Year, Open-Label Trial of Valbenazine in Participants With Tardive Dyskinesia. Poster presented at the 2017 American College of Neuropsychopharmacology Annual Congress, Palm Springs, CA.

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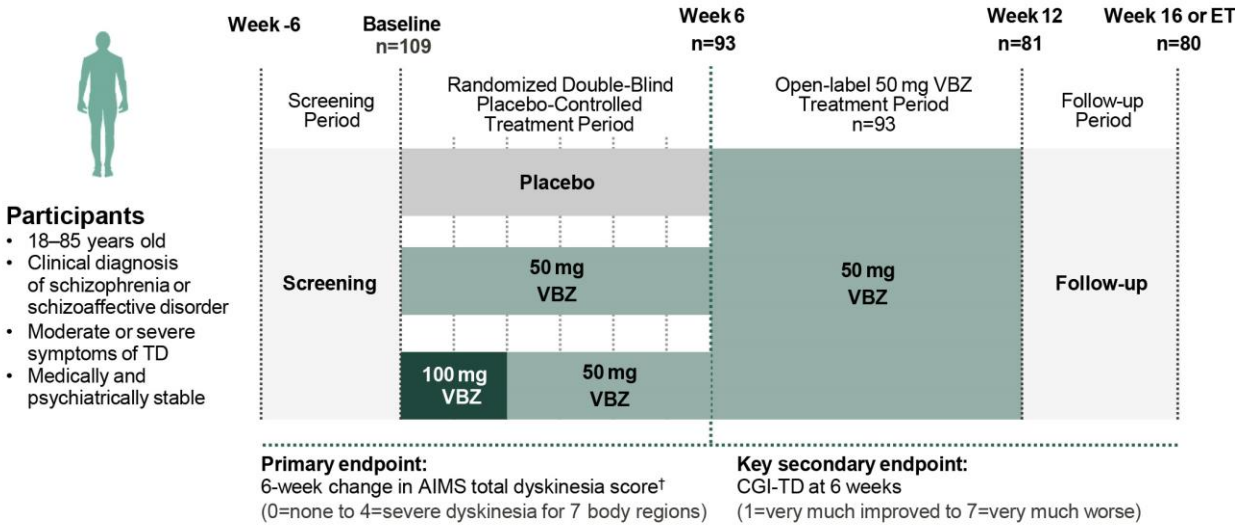
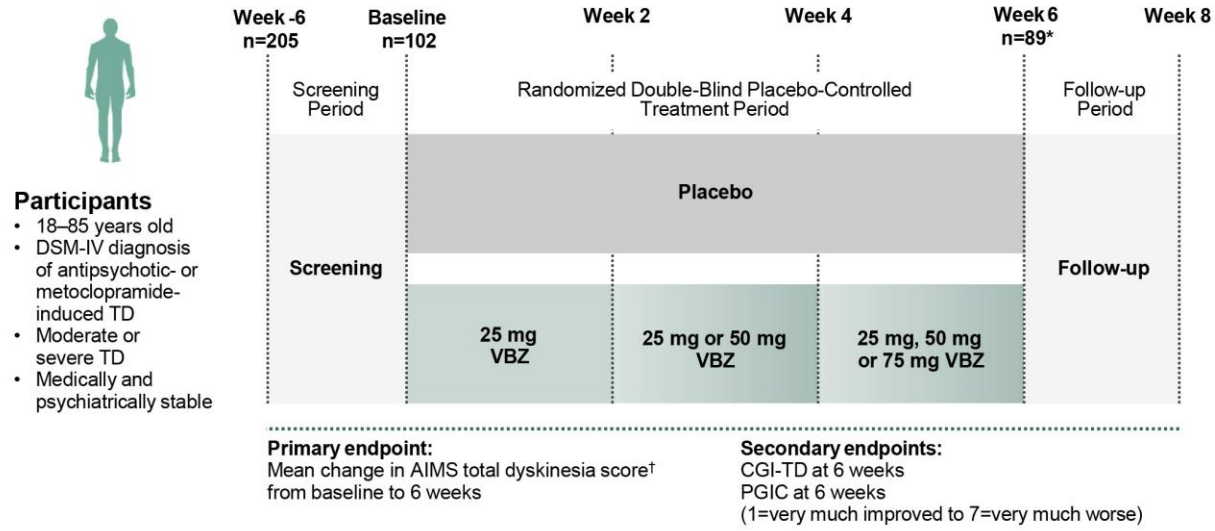
Appendix (Study Designs)

Appendix Figure 1. KINECT 1 Study Design



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change–Tardive Dyskinesia; ET, early termination; TD, tardive dyskinesia; VBZ, valbenazine.
*109 participants completed the double-blind study period, and 93 continued into the open-label extension period.
†Rated by onsite investigators.
Participants were randomized 1:1:2 to 1 of 3 treatment groups: VBZ 50 mg once daily for 6 weeks, VBZ 100 mg once daily for 2 weeks followed by 50 mg once daily for 4 weeks or matching placebo. All participants completing the 6-week double-blind phase were eligible for continuation to a 6-week open-label treatment phase with once-daily 50 mg VBZ.

Appendix Figure 2. KINECT 2 Study Design



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change–Tardive Dyskinesia; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; PGIC, Patient Global Impression of Change; TD, tardive dyskinesia; VBZ, valbenazine.
*Final intent-to-treat analysis population; 76% of participants in the VBZ arm and 80% in the placebo arm reached the maximum 75-mg dose.
†Rated by the central video scorers blinded to treatment arm and study visit sequence.
Participants were randomized 1:1 to receive either placebo or VBZ, beginning at 25 mg once daily. VBZ dose was escalated by 25 mg at Weeks 2 and 4 to a maximum of 75 mg once daily, contingent upon investigator's clinical judgment and participant's response to and toleration of VBZ starting dose.

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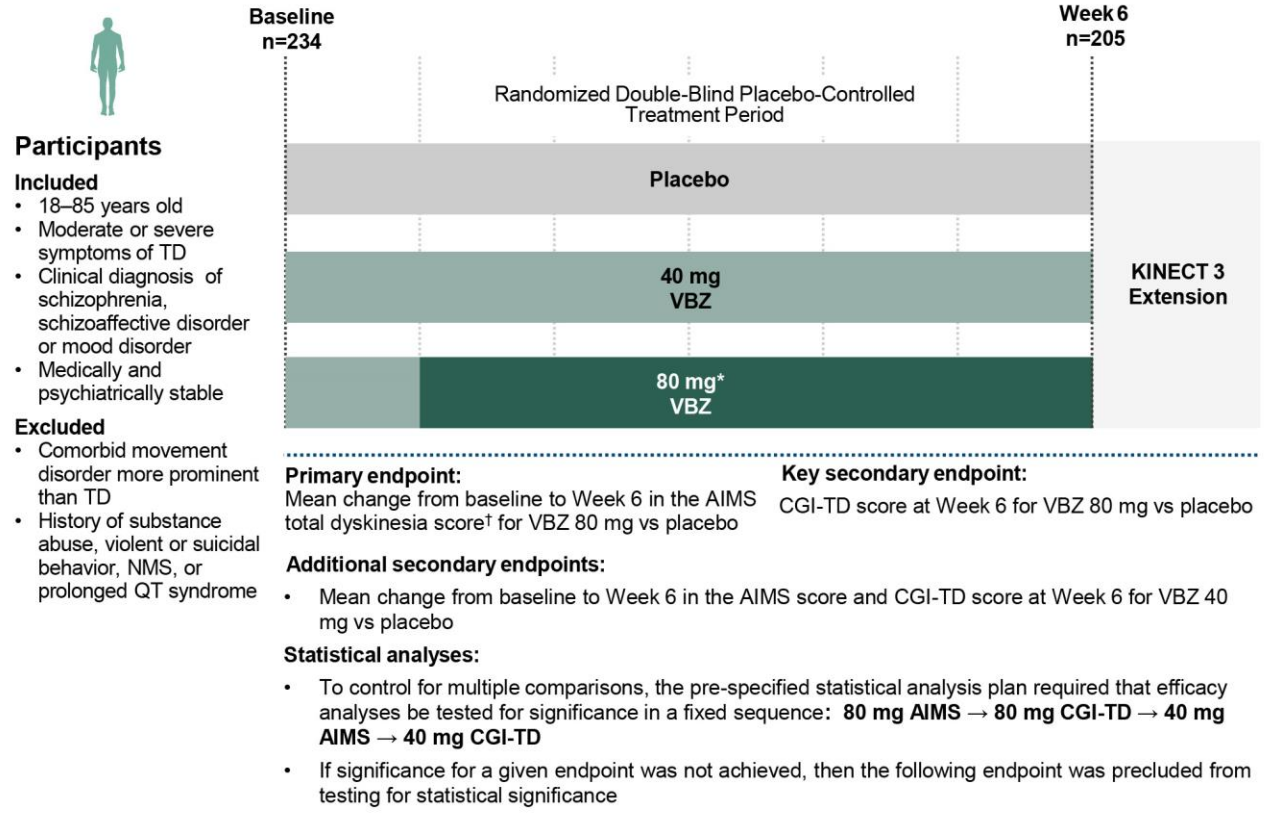
Appendix Figure 3. KINECT 3 Study Design



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; NMS, neuroleptic malignant syndrome; TD, tardive dyskinesia; VBZ, valbenazine.
*80-mg group received 40 mg for the first week.
†Sum of Items 1-7; scored by consensus of 2 blinded, central video AIMS raters.

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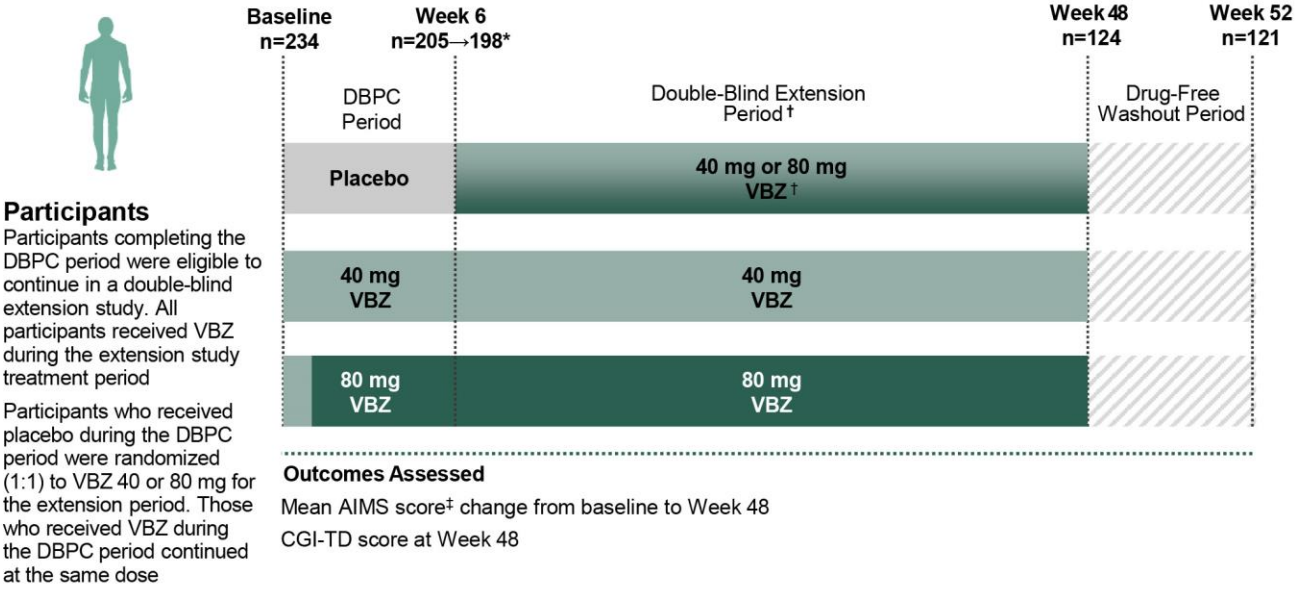
Appendix Figure 4. KINECT 3 Double-Blind Extension Study Design



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; DBPC, double-blind placebo-controlled; TD, tardive dyskinesia; VBZ, valbenazine.
*205 participants completed the DBPC period and 198 entered the extension period, with 101 receiving VBZ 80 mg and 97 receiving VBZ 40 mg during the extension period.
†All dosing started at 40 mg and increased to 80 mg after the first week.
‡Scored by consensus of two blinded, central video AIMS raters.

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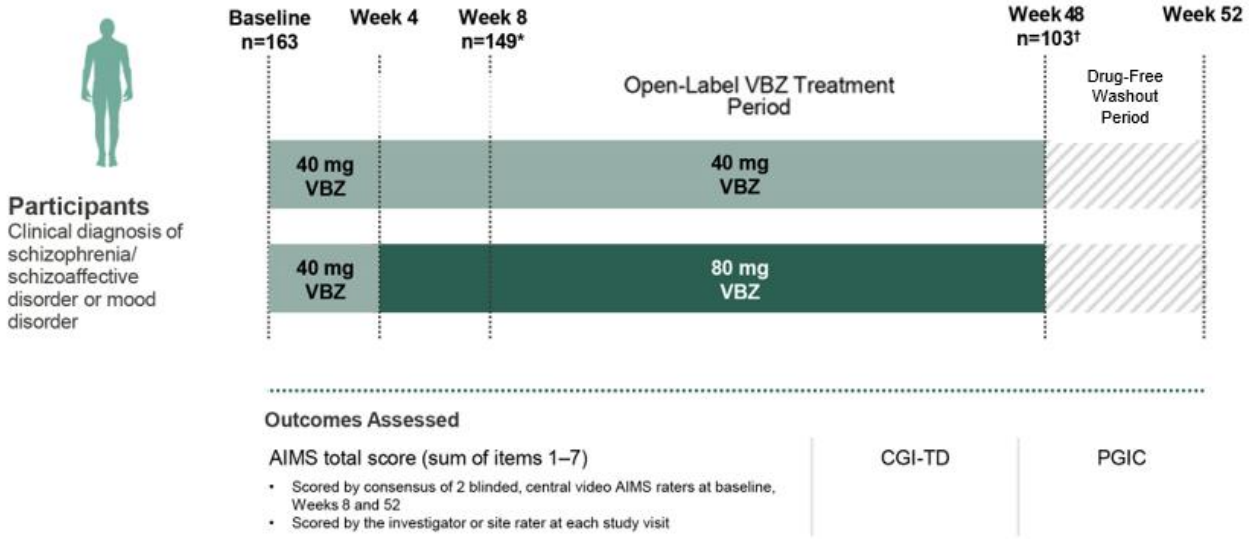
Appendix Figure 5. KINECT 4 Study Design



AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change; TEAE, treatment-emergent adverse event; VBZ, valbenazine.
*40 mg, n=33; 80 mg, n=105; 80/40 mg, n=11.
†40 mg, n=20; 80 mg, n=74; 80/40 mg, n=9.

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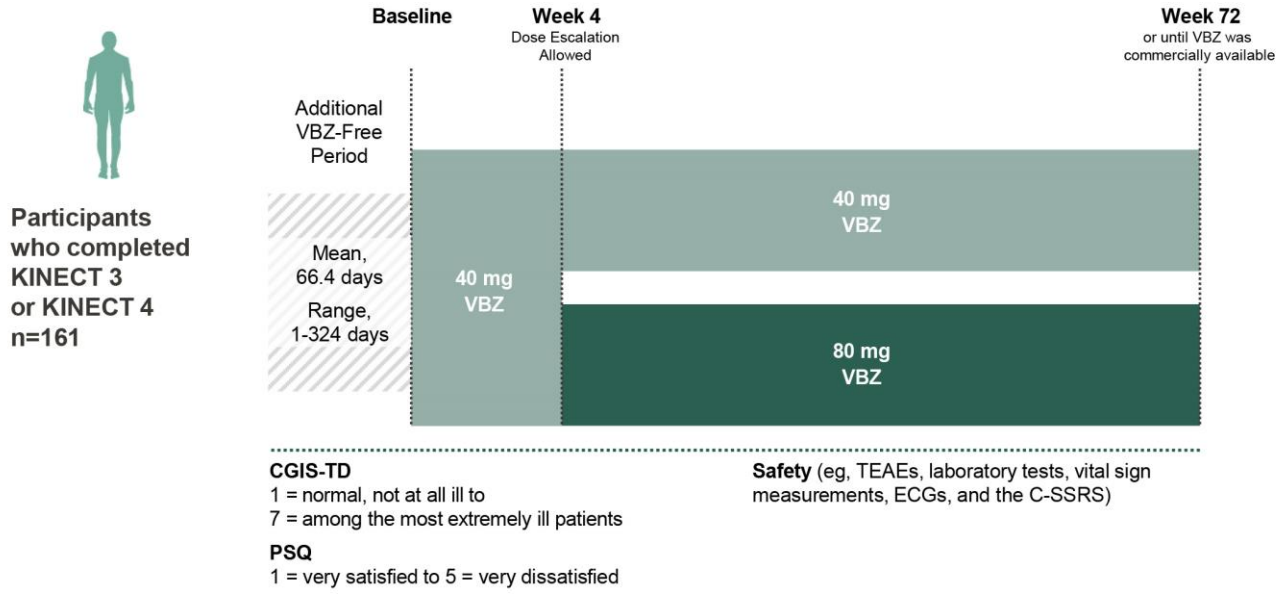
Appendix Figure 6. 1506 Study Design



CGIS-TD, Clinical Global Impression of Severity-Tardive Dyskinesia; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; PSQ, Patient Satisfaction Questionnaire; TEAE, treatment-emergent adverse event; VBZ, valbenazine.
All rollover study participants received once-daily VBZ 40 mg for 4 weeks. At Week 4, dosing was escalated to 80 mg based on tolerability and clinical assessment of TD. A 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. Analyses were conducted in 160 participants who received VBZ 40 mg (n=35), 80 mg (n=117), or 80 mg with dose reduction (80/40 mg, n=8). One participant without postbaseline data was excluded from the analyses.