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Long-term Safety 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 long-term safety data 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]

The information outlined in this letter is not inclusive of all safety information related to valbenazine in patients with TD, such as the short-term safety data. For information regarding the full safety profile of valbenazine, please refer to the attached Important Safety Information and the FDA-approved full Prescribing Information.

An extensive clinical program has been conducted to investigate the long-term safety of valbenazine, including two Phase 3 studies (KINECT® 3 long-term extension and KINECT® 4) and one Phase 3b rollover study (1506). The purpose of this document is to respond to your request for a brief summary of the long-term safety data for valbenazine.

Summary of Key Safety Outcomes

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KINECT 3: Phase 3 Double-Blind Valbenazine Extension Period[2,3]

Study Design

KINECT 3 was a randomized, double-blind, placebo-controlled (DBPC) Phase 3 study designed to assess the efficacy, safety, and tolerability of valbenazine in the treatment of TD. Participants (n=234) were randomized 1:1:1 to receive placebo (PBO), valbenazine 40 mg, or valbenazine 80 mg once daily for 6 weeks. Participants who completed the DBPC period continued with a 42-week double-blind valbenazine extension (VE) period and a 4-week follow-up (**Appendix Figure 1**). Those initially randomized to placebo were re-randomized 1:1 to once-daily valbenazine 80 or 40 mg and those initially randomized to valbenazine 80 or 40 mg continued at the same dose.

Participants

Demographics were similar across treatment groups (**Table 1**). Of the 234 randomized participants, 205 participants completed the 6-week DBPC period. Of these 205 participants, 198 entered the VE period, 124 completed the VE period, and 121 completed follow-up.[3]

Table 1. Baseline Characteristics (ITT Population)

	Placebo (n=76)	Valbenazine 40 mg (n=72)	Valbenazine 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.

Safety

During the extension period (post-Week 6 to Week 48), 69.2% of participants had ≥1 treatment-emergent adverse event (TEAE) and 14.6% had ≥1 serious adverse event (AE). Rates of commonly reported TEAEs are summarized in **Table 2**. There were no clinically important changes in clinical laboratory, vital signs, or electrocardiogram (ECG) parameters during the extension treatment or washout periods.

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Table 2. Commonly Reported TEAEs

TEAEs, n (%)	Valbenazine 40 mg (n=97)	Valbenazine 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 3, Open-Label, Long-Term Study[4,5]

Study Design

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KINECT 4 was an open-label, long-term Phase 3 study to evaluate 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 2**). Valbenazine was initiated at 40 mg for the first 4 weeks; afterwards, dosing could be escalated to 80 mg if both of the following conditions were met: CGI-TD score of ≥3 ("minimally improved" to "very much worse"), and acceptable safety/tolerability with 40 mg based on investigator judgement.

Participants

Baseline characteristics were similar across treatment groups. Of the 163 participants included in the analyses, 149 participants reached the Week 8 visit and 103 participants reached the Week 48 visit.

Safety

Rates of TEAEs during the study are shown in **Table 4**. 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 4. TEAE (Total* and Most Common)

TEAEs, 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 3b, Long-Term, Open-Label Rollover Study[6]

Study Design

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Study 1506 was an open-label, rollover Phase 3b study that enrolled participants who completed KINECT 3 or KINECT 4 (**Appendix Figure 3**). 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. Mean (SD) total duration of valbenazine exposure was 19.7 (3.4) months (range, 9.9–26.9 months).

Safety

Incidence of TEAEs before and after Week 4 (dose escalation) are shown in **Table 5**. 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 5. TEAE Rates Before and After Week 4*

	Baseline to Week 4†	Week 4 to End of Study
TEAEs, n (%)	**Valbenazine 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.

Pooled Long-Term Safety Data[7]

Study Design

A long-term exposure (LTE) safety analysis included valbenazine -treated participants from 3 studies: KINECT, KINECT 3, and KINECT 4 (**Appendix Figure 4**). The pooled LTE 80 mg group combined data from the 80 mg arms of KINECT 3 and KINCET 4. The pooled LTE 40 mg group included participants

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from the 40 mg groups in KINECT 3 and KINECT 4 as well as the 50 mg group from KINECT (including patients who initially received 2 weeks of 100 mg).

Participants

430 participants were included in the LTE safety population (KINECT, n=46; KINECT 3, n=220; KINECT 4, n=164). The mean (SD) duration of valbenazine exposure in all participants was 204 days (119 days); median duration of exposure was 225 days (range, 1-356 days). Demographics and participant disposition were similar between the pooled treatment groups.

Safety

Safety parameters included AEs, vital signs, ECG, and laboratory tests. Participants were assessed for maintenance of psychiatric stability throughout the studies using the following scales: Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS) and Columbia-Suicide Severity Rating Scale (C-SSRS). All outcomes were analyzed descriptively.

The overall incidence of TEAEs in the LTE safety population are shown in **Table 6**. No notable ECG changes were found, including the 81% of participants who were taking concomitant medications with a known potential to prolong the QT interval. Laboratory parameters were similar across treatment groups; no clinically relevant changes were identified, including liver function tests and metabolic parameters. Mean psychiatric scales scores generally remained stable in participants with schizophrenia/ schizoaffective disorder (PANS, CDSS) or mood disorder (YMRS, MADRS) during long-term valbenazine treatment.

Table 6. AE (Safety Population)

	Valbenazine 40 mg (n=200)	Valbenazine 80 mg (n=230)	All Participants (n=430)
Summary of AEs, %			
Any TEAE	61.0	71.3	66.5
Any serious AE*	11.5	16.5	14.2
Discontinuation due to AE	16.0	13.5	14.7
AE leading to dose reduction	5.0	8.3	6.7
TEAEs by preferred term, %†			
Headache	7.0	8.3	7.7
Urinary tract infection	7.5	7.4	7.4
Somnolence	7.5	5.2	6.3
Fatigue	7.0	3.5	5.1

AE, adverse event; TEAE, treatment-emergent adverse event.
*Serious AEs that occurred in ≥1% of all subjects were schizophrenia (1.2%) and suicidal ideation (1.2%).
†Reported in ≥5% of all valbenazine-treated subjects.

For a more complete description of these analyses, please see the references and respective links below.

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.

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References

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
2. 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.
3. 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.
4. 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.
5. 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.
6. Lindenmayer JP, et al. A long-term, open-label study of valbenazine for tardive dyskinesia. *CNS Spectrums.* 2020:1-9.
7. Remington G, et al. Safety and tolerability of valbenazine in subjects with tardive dyskinesia: results of long-term exposure data from three studies. Poster presented at the 55th Annual Meeting of the American College of Neuropsychopharmacology; December 4-8, 2016; Hollywood, FL.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. INGREZZA [Important Safety Information]. San Diego, CA: Neurocrine Biosciences, Inc.
C. 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.
D. Remington G, et al. Safety and tolerability of valbenazine in subjects with tardive dyskinesia: results of long-term exposure data from three studies. Poster presented at the 55th Annual Meeting of the American College of Neuropsychopharmacology; December 4-8, 2016; Hollywood, FL.

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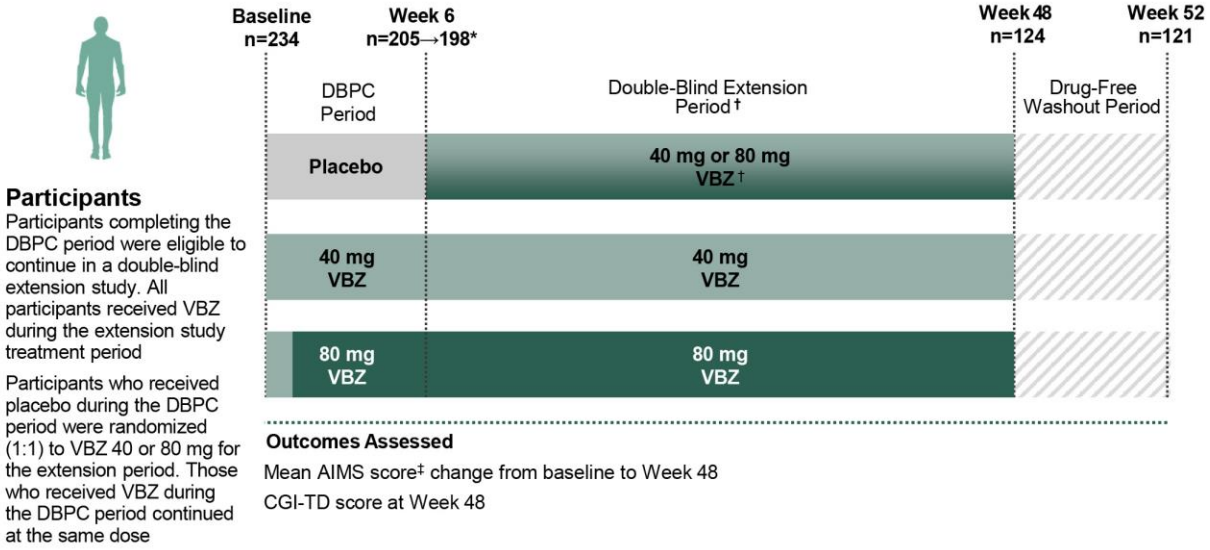
Appendix

Appendix Figure 1. 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 2 blinded, central video AIMS raters.

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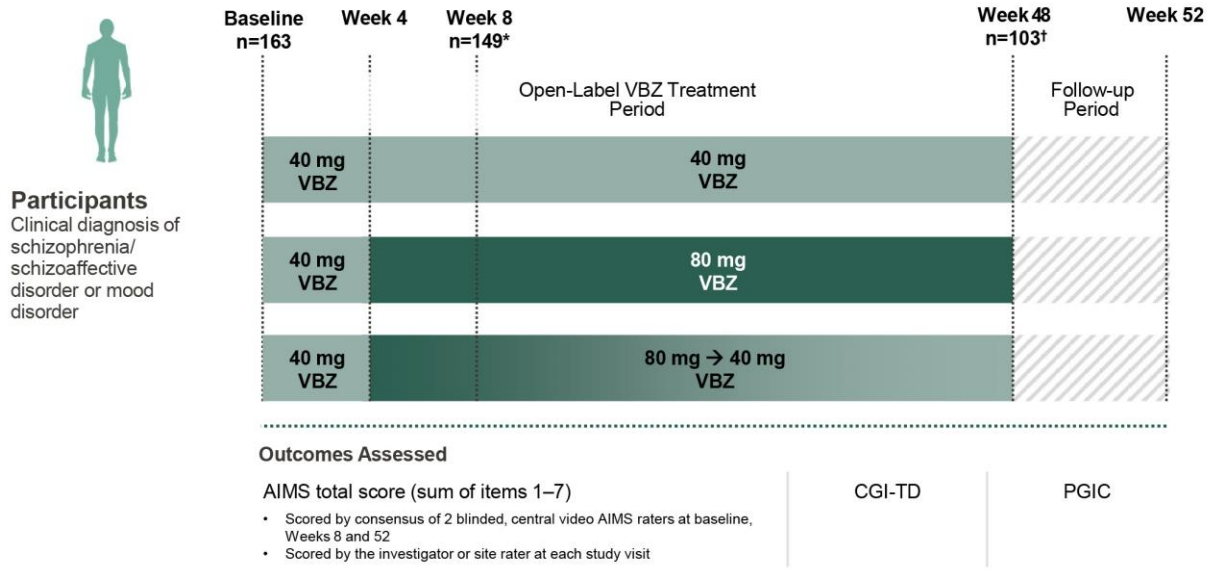
Appendix Figure 2. KINECT 4 Study Design



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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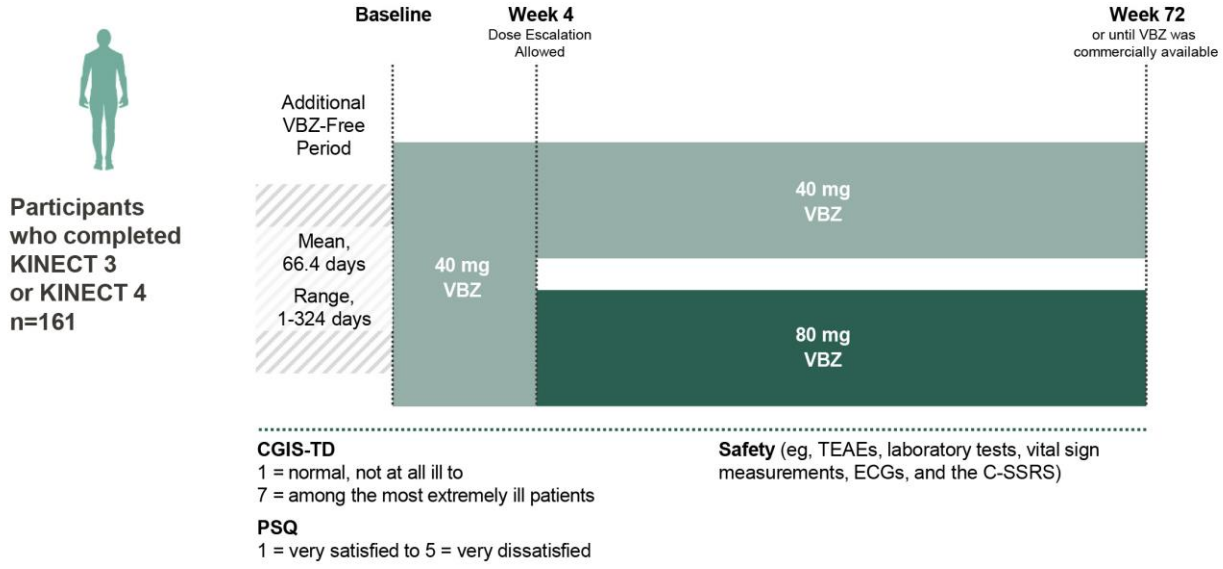
Appendix Figure 3. 1506 Study Design



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.

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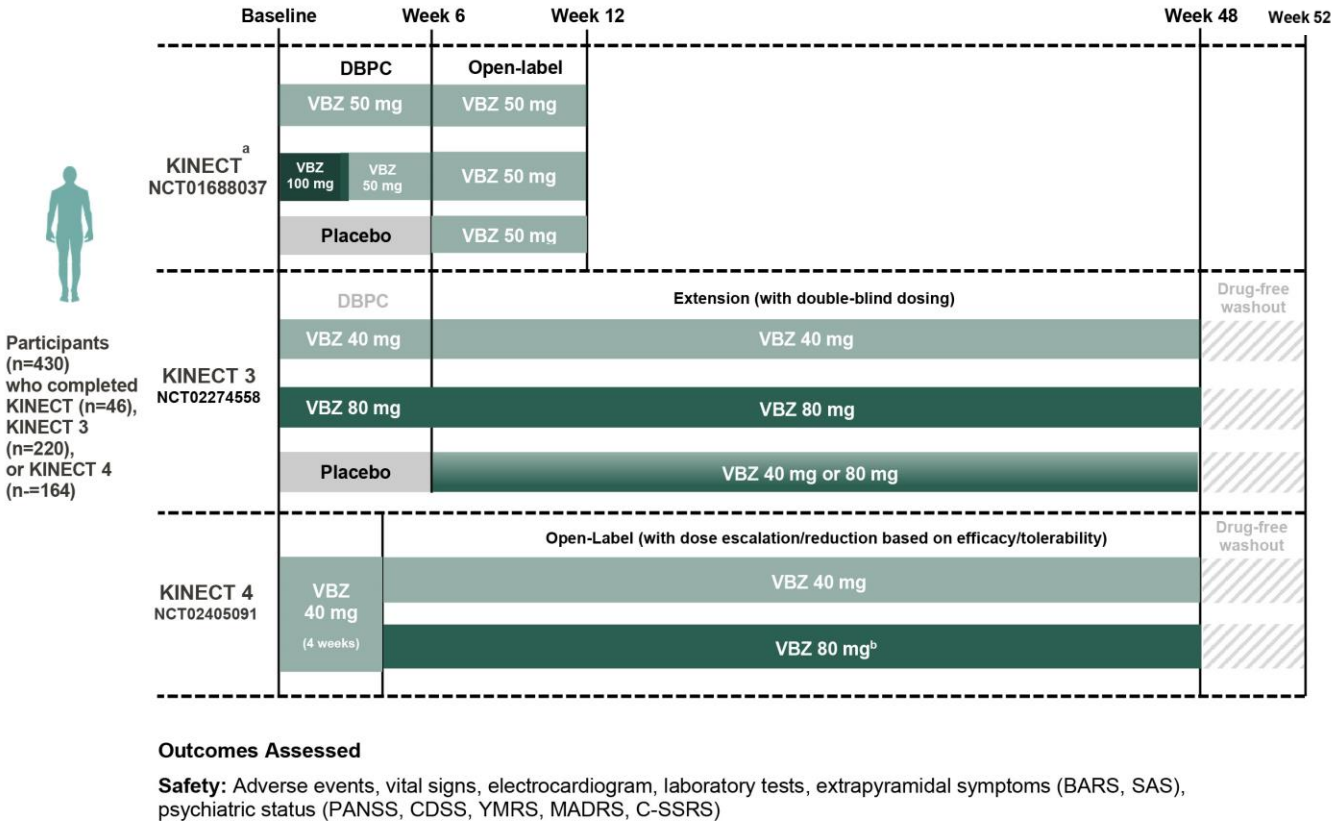
Appendix Figure 4. AE (Safety Population)



Outcomes Assessed

Safety: Adverse events, vital signs, electrocardiogram, laboratory tests, extrapyramidal symptoms (BARS, SAS), psychiatric status (PANSS, CDSS, YMRS, MADRS, C-SSRS)

[a]KINECT: second treatment arm received 100 mg for 2 weeks; this study also had a 4-week washout period.
[b]KINECT 4: includes participants who had a dose reduction to 40 mg due to tolerability issues.
DBPC, double-blind placebo-controlled; VBZ, valbenazine.