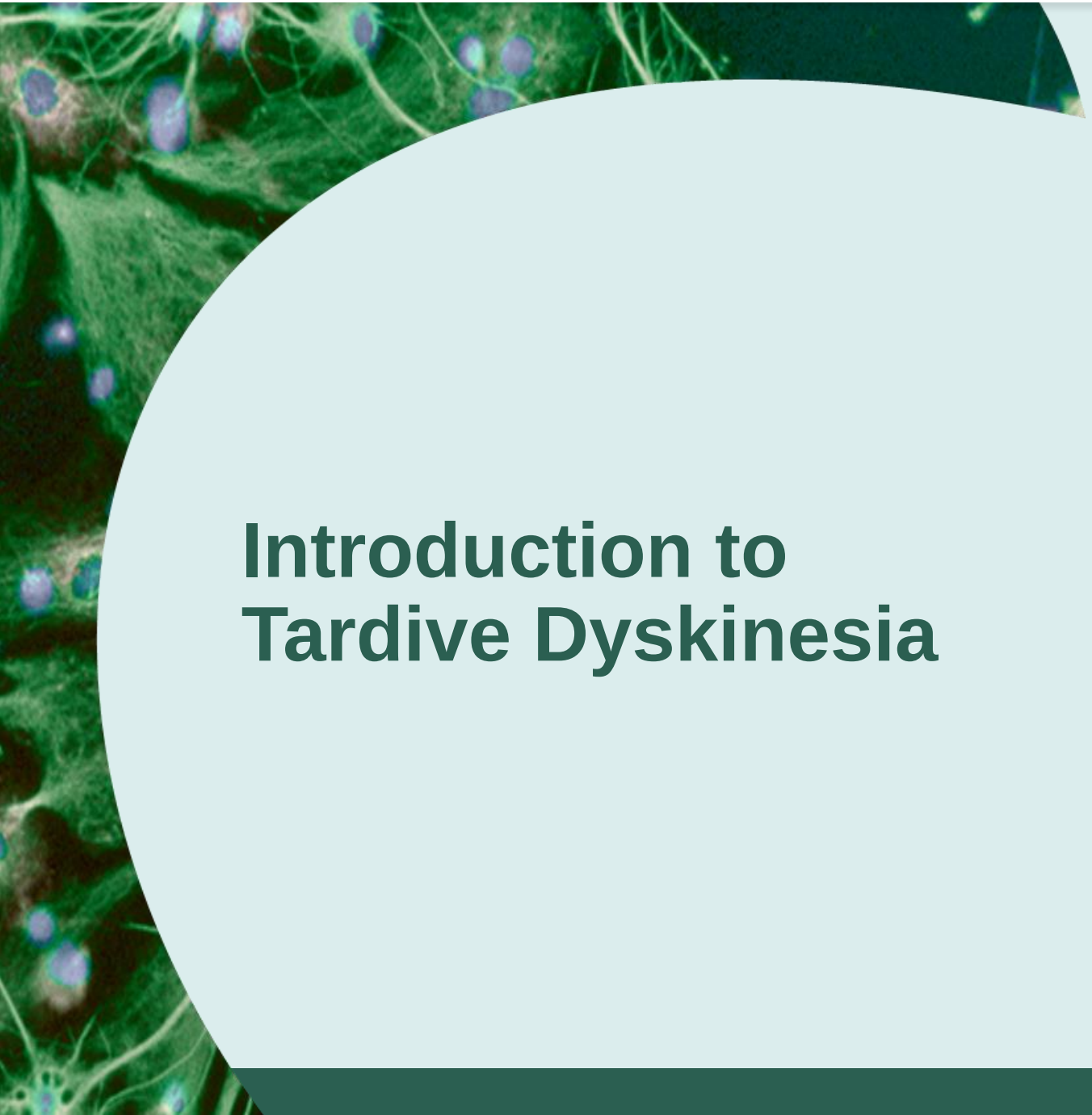
Valbenazine in Tardive Dyskinesia

NEUROCRINE® BIOSCIENCES

MED-MSL-TD-US-0135_v8

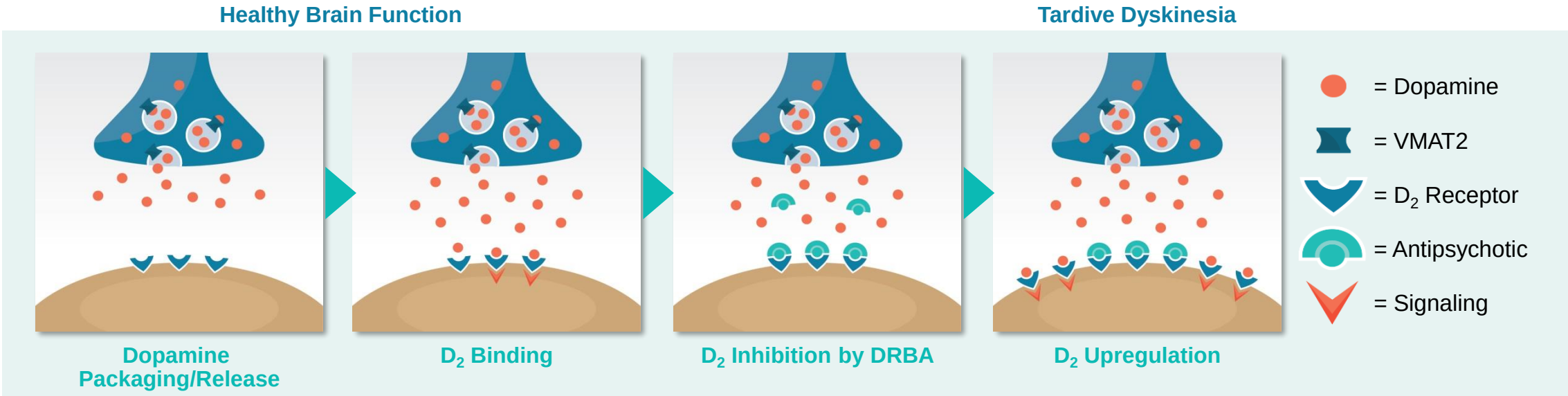
Table of Contents



Introduction to Tardive Dyskinesia

TD Pathophysiology

- The mechanism underlying TD is complex, and the exact cause has not been fully elucidated[1-4]
- A leading theory is the upregulation and subsequent hypersensitivity of brain dopamine D_2 receptors following prolonged exposure to DRBAs[1]
- Additional hypotheses include DRBA-induced:
  - Oxidative stress from free radical formation[2]
  - Dysfunction of GABA and/or serotonin pathways[3,4]



TD Mechanism of Disease Video

DRBA, dopamine receptor–blocking agent; GABA, gamma-aminobutyric acid; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter type 2.

1. Klawans H, et al. *Acta Neurol Scand*. 1970;46(4):409-441. 2. Pai BN, et al. *Biol Psychiatry*. 1994;36(7):489-491. 3. Segman RH, et al. *Mol Psychiatry*. 2001;6(2):225-229. 4. Gittis AH, et al. *J Neurosci*. 2011;31(44):15727-15731.

TD is a Clinically Distinct, Delayed DRBA-induced Movement Disorder[1]

Defined as abnormal, involuntary movements of the tongue, jaw, trunk, or extremities that develop in association with medications that block postsynaptic dopamine receptors

TD movements may be:*

Choreiform	Rapid, jerky, nonrepetitive
Athetoid	Slow, sinuous, continual
Semirhythmic	E.g., stereotypies

DRBAs can include:

- FGAs
- SGAs
- Gastrointestinal medications, such as metoclopramide

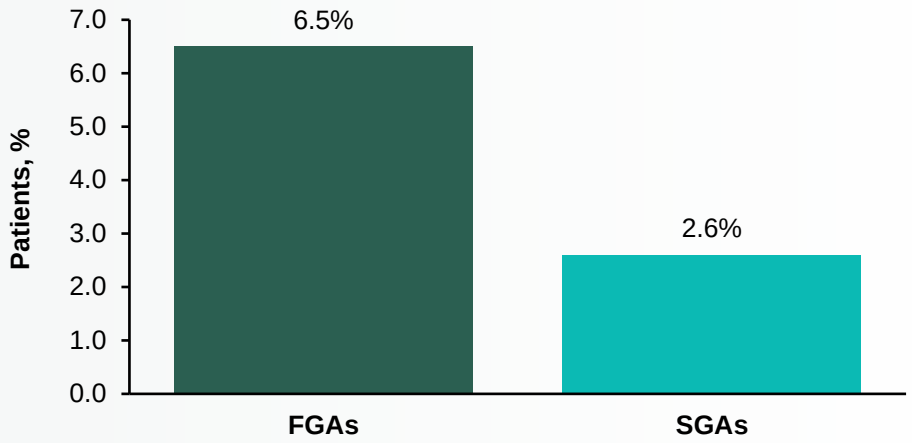
Jaw, Tongue, Neck → **OBL and Legs** → **Jaw, Hand, Face** → **Leg, Shoulder, Face**

DRBA, dopamine receptor–blocking agent; FGA, first-generation antipsychotic; OBL, oral-buccal-lingual; SGA, second-generation antipsychotic; TD, tardive dyskinesia.
*Movements are distinctly different from the rhythmic tremors (3–6 Hz) commonly seen in drug-induced parkinsonism.[1]

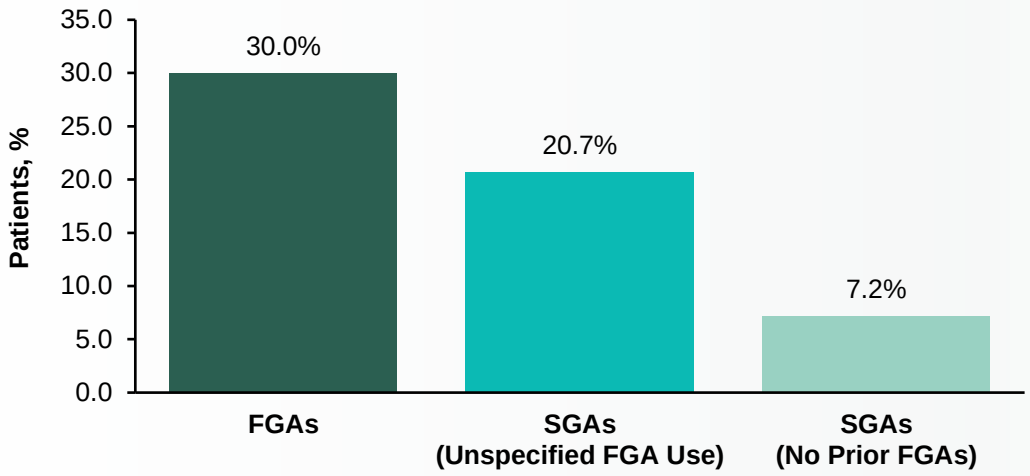
1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision.* American Psychiatric Association; 2022.

TD is Associated With Prolonged DRBA Treatment

TD Annual Incidence[1]*



TD Prevalence[2]†



~5 million patients in the United States are treated with antipsychotics[3]
≥600,000 patients may have TD[3,4]‡

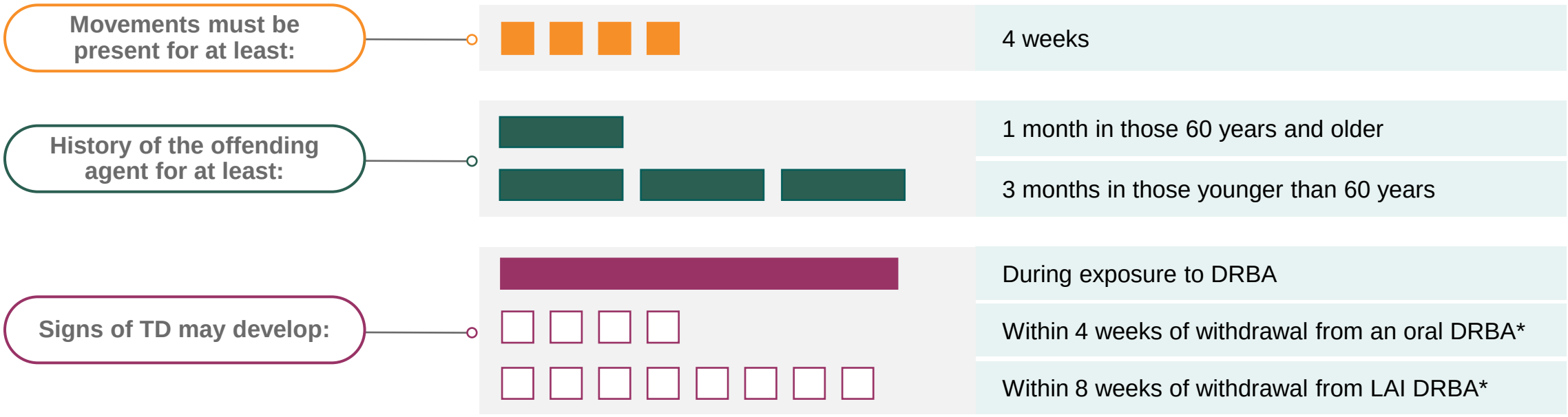
Trends in Antipsychotic Prescribing

Risk Factors for TD

DRBA, dopamine receptor–blocking agent; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; TD, tardive dyskinesia.
*2018 meta-analysis of 57 randomized controlled trials (FGA-SGA studies, N=10,706; SGA-SGA studies, N=9153). †2017 meta-analysis of 41 studies (N=11,493). ‡Estimate from a 2014 analysis of prescriptions and incidence rates.
1. Carbon M, et al. *World Psychiatry*. 2018;17(3):330-340. 2. Carbon M, et al. *J Clin Psychiatry*. 2017;78(3):e264-e278. 3. Cloud LJ, et al. *Neurotherapeutics*. 2014;11:166-176. 4. Data on file. Neurocrine Biosciences, Inc.

Diagnosis of TD

- Health care providers use clinical evaluation and medical history to diagnose TD
- TD may appear in patients also experiencing other DRBA-induced movement disorders



DRBA, dopamine receptor–blocking agent; TD, tardive dyskinesia; LAI, long-acting injectable.
*Dyskinesia may remit with continued withdrawal. A diagnosis of TD may be warranted if the dyskinesia persists for at least 4 weeks.
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision*. American Psychiatric Publishing; 2022.

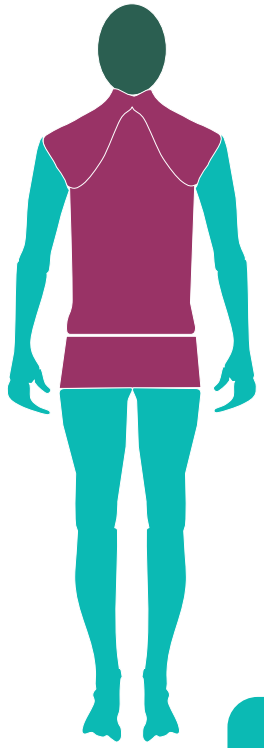
Scoring AIMS

AIMS is a 12-item, clinician-rated scale used to assess TD severity

	Facial and Oral Movements	None	Minimal	Mild	Moderate	Severe
1.	Muscles of facial expression	0	1	2	3	4
2.	Lips and perioral area	0	1	2	3	4
3.	Jaw	0	1	2	3	4
4.	Tongue	0	1	2	3	4
	Extremity Movements	**None**	**Minimal**	**Mild**	**Moderate**	**Severe**
5.	Upper (arms, wrists, hands, fingers)	0	1	2	3	4
6.	Lower (legs, knees, ankles, toes)	0	1	2	3	4
	Trunk Movements	**None**	**Minimal**	**Mild**	**Moderate**	**Severe**
7.	Neck, shoulders, hips	0	1	2	3	4

AIMS Total Dyskinesia Score=Sum of Items 1–7

8. Global severity of abnormal movements
9. Incapacitation
10. Awareness
11–12. Dental status



Screening Guidelines

Scoring AIMS Patient Videos

AIMS, Abnormal Involuntary Movement Scale; TD, tardive dyskinesia.
0=no dyskinesia; 1=low amplitude, present during some, but not most of, the exam; 2=low amplitude and present during most of the exam (or moderate amplitude and present during some of the exam); 3=moderate amplitude and present during most of exam; or 4=maximal amplitude and present during most of exam.

Guy W. *ECDEU Assessment Manual for Psychopharmacology*: Revised 1976. (DHEW publication number ADM 76-338). National Institute of Mental Health, Psychopharmacology Research Branch; 1976:534-537.

2020 APA Guideline: TD Recommendations

2018 Systematic Review[1]

Intervention	Category	Conclusion
VBZ	LEVEL A	Recommended as **first-line treatment**
Deutetrabenazine	LEVEL A	Recommended as **first-line treatment**

2020 APA Guideline Recommendations[2]

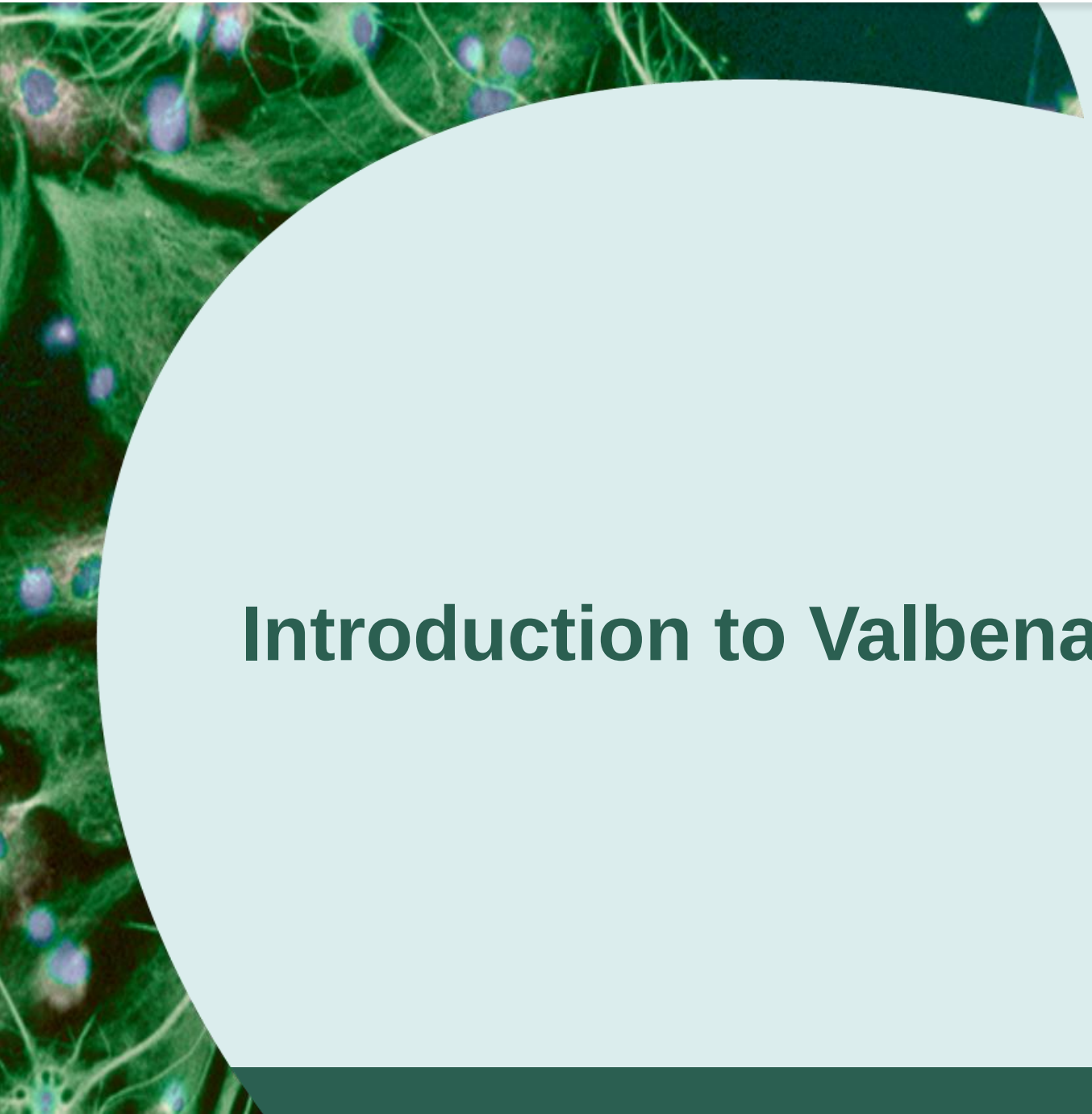
Intervention	Category	Conclusion
Reversible VMAT2 inhibitor for treatment of TD	1B	**Recommended in moderate to severe, or disabling TD**
	N/A*	**Can be considered in mild TD** based on factors such as patient preference, associated impairment, or effect on psychosocial functioning

VMAT2 inhibitors are recommended and/or considered in the full severity spectrum of TD

2018 Review Treatment Algorithm

AAN, American Academy of Neurology; APA, American Psychiatric Association; DRBA, dopamine receptor–blocking agent; N/A, not available; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter type 2; VBZ, valbenazine. 2013 AAN guidelines were published before available treatments were approved for adults with TD. 2018 systematic review aimed to update the evidence-based recommendations and provide a practical algorithm for treatment of TD.
*GRADE ratings were only assigned for primary guideline statements.

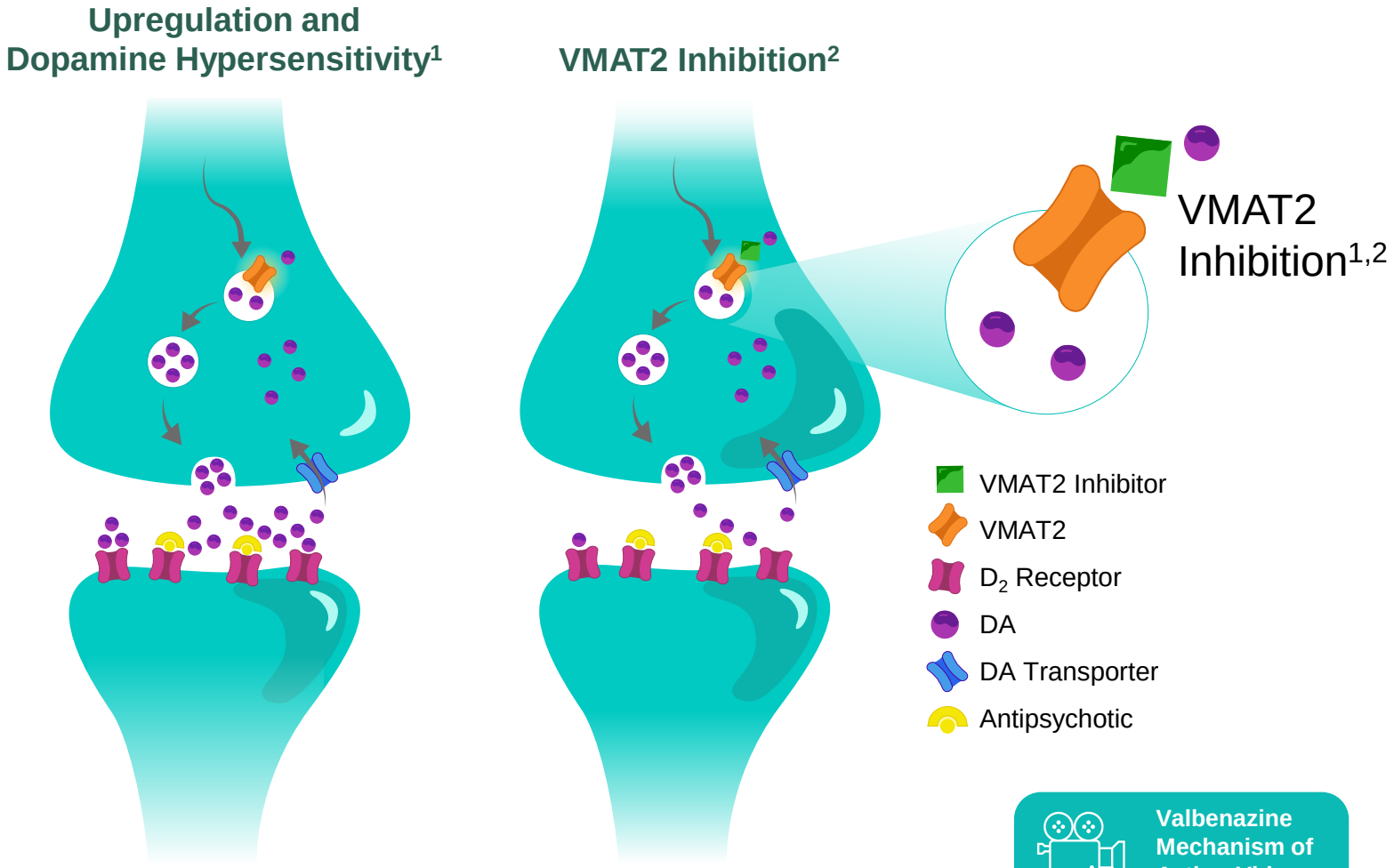
1. Bhidayasiri R, et al. *J Neurol Sci*. 2018;389:67-75. 2. American Psychiatric Association. Clinical practice guidelines for treatment of patients with schizophrenia. Accessed on March 8, 2023. https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841.



Introduction to Valbenazine

Valbenazine Mechanism of Action

The mechanism of action of valbenazine in the treatment of TD is unclear, but is thought to be mediated through the reversible inhibition of VMAT2[2]



Valbenazine Mechanism of Action Video

TD, tardive dyskinesia; VBZ, valbenazine; VMAT2, vesicular monoamine transporter type 2.

1. Margolese HC, et al. *Can J Psychiatry*. 2005;50:541-547. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., 2021.

Valbenazine Overview

Valbenazine[1]

Typical dosage range	40, 60, 80 mg, 1 capsule once daily
2 Formulations	INGREZZA® and INGREZZA® SPRINKLE
Renal Impairment or **Geriatric Use**	No dose adjustment
Hepatic Impairment	Maximum 40mg daily
Effect of Food	Taken with or with food
Single Active Metabolite	[+]-α-HTBZ, Selective for VMAT2 only, with no appreciable binding affinity for dopaminergic, serotonergic, adrenergic, or histaminergic receptors[2]
Elimination half-life	15–22 hours

HTBZ, dihydrotetrabenazine; VBZ, valbenazine; VMAT2, vesicular monoamine transporter type 2.

1. Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia*. 3rd ed. Washington, DC: American Psychiatric Association; 2020. https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841. Accessed April 20, 2021. 2. INGREZZA® (valbenazine) [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.; 2021.

MIDD Modeling & Simulation

INGREZZA and INGREZZA SPRINKLE Important Safety Information

Depression and Suicidality in Patients with Huntington's Disease: VMAT2 inhibitors, including INGREZZA and INGREZZA SPRINKLE, can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidal ideation, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidal ideation and behavior and instruct them to report behaviors of concern promptly to the treating physician. Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.

CONTRAINDICATIONS

INGREZZA and INGREZZA SPRINKLE are contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA or INGREZZA SPRINKLE.

WARNINGS & PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions, including cases of angioedema involving the larynx, glottis, lips, and eyelids, have been reported in patients after taking the first or subsequent doses of INGREZZA. Angioedema associated with laryngeal edema can be fatal. If any of these reactions occur, discontinue INGREZZA or INGREZZA SPRINKLE.

Somnolence and Sedation: INGREZZA and INGREZZA SPRINKLE can cause somnolence and sedation. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA or INGREZZA SPRINKLE.

Drug Interactions

NMS, neuroleptic malignant syndrome;TD, tardive dyskinesia; VBZ, valbenazine; VMAT2, vesicular monoamine transporter type 2.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

INGREZZA and INGREZZA SPRINKLE Important Safety Information

QT Prolongation: INGREZZA and INGREZZA SPRINKLE may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA and INGREZZA SPRINKLE should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission, including INGREZZA. The management of NMS should include immediate discontinuation of INGREZZA or INGREZZA SPRINKLE, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If treatment with INGREZZA or INGREZZA SPRINKLE is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Parkinsonism: INGREZZA and INGREZZA SPRINKLE may cause parkinsonism. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA or INGREZZA SPRINKLE treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS

The most common adverse reaction in patients with tardive dyskinesia (≥5% and twice the rate of placebo) is somnolence. The most common adverse reactions in patients with chorea associated with Huntington's disease ((≥5% and twice the rate of placebo) are somnolence/lethargy/sedation, urticaria, and insomnia.

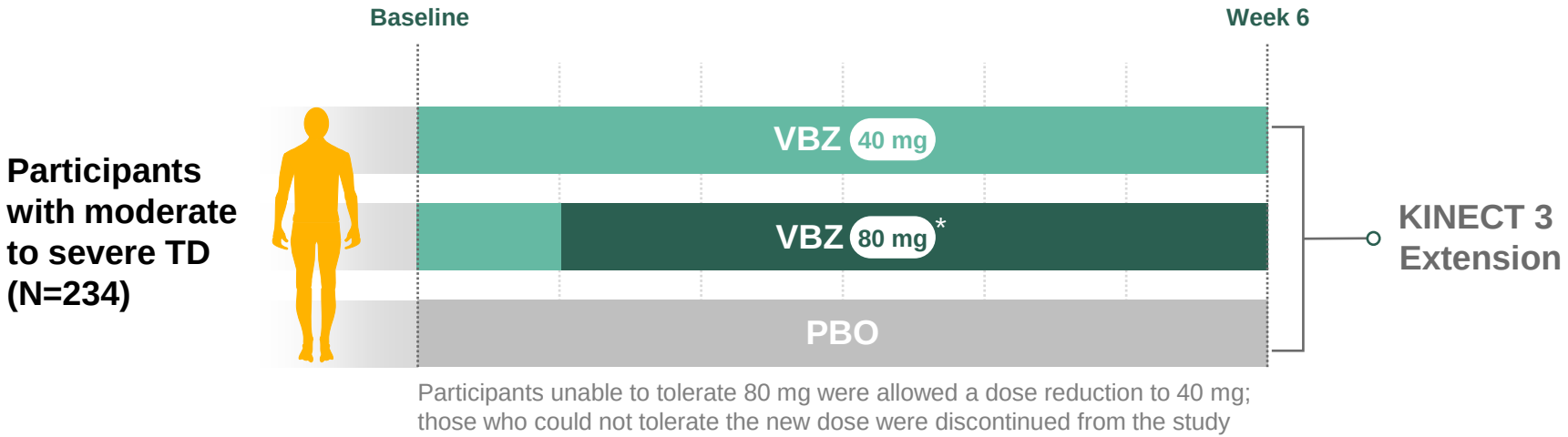
NMS, neuroleptic malignant syndrome; VMAT2, vesicular monoamine transporter 2.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

KINECT 3 (NCT02274558): Double-blind, Placebo-controlled Phase 3 Study

KINECT 3: Study Design

Randomized, double-blind, placebo-controlled, fixed-dose study



Participants unable to tolerate 80 mg were allowed a dose reduction to 40 mg; those who could not tolerate the new dose were discontinued from the study

Primary Endpoint

Change from baseline to Week 6 on the AIMS total dyskinesia score (scored by blinded central video raters)

The prespecified SAP required that efficacy analyses be tested for significance in a fixed sequence:

80 mg AIMS → 80 mg CGI-TD → 40 mg AIMS → 40 mg CGI-TD

Secondary Endpoint

CGI-TD

If significance for a given endpoint was not achieved, then the following endpoint was precluded from testing for statistical significance

AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PBO, placebo; SAP, statistical analysis plan; TD, tardive dyskinesia; VBZ, valbenazine.
*80-mg group received 40 mg for the first week.
Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.

KINECT 3: Eligibility Criteria[1,2]

Key inclusion criteria

- Age 18–85 years
- Schizophrenia, schizoaffective disorder, or mood disorder* diagnosed ≥3 months before screening
- TD ≥3 months before screening
- Moderate or severe TD based on qualitative assessment of screening video
- Stable dose of maintenance medications for psychiatric conditions
- Clinically stable medical conditions

Key exclusion criteria

- BPRS total score ≥50 at screening
- Significant suicidal ideation or behavior
- History of prolonged QT syndrome
- For participants with diagnosed schizophrenia or schizoaffective disorder
  - CDSS total score ≥10
  - PANSS total score ≥70
- For participants with diagnosed mood disorder
  - YMRS total score >10
  - MADRS [SIGMA] total score >13
  - Hospitalization for BD or MDD within 6 months before screening
  - Mood episodes† within 2 months before screening
  - History of rapid or ultra-rapid cycling

BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; MADRS [SIGMA], Montgomery-Asberg Depression Rating Scale using the Structured Interview Guide; MDD, major depressive disorder; PANSS, Positive and Negative Syndrome Scale; TD, tardive dyskinesia; YMRS, Young Mania Rating Scale.
*Mood disorder primarily includes BDs and depressive disorders. †Including hypomania, mania, depressive, etc.
1. Hauser RA, et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Data on file. Neurocrine Biosciences, Inc.

KINECT 3: Baseline Characteristics[1,2]

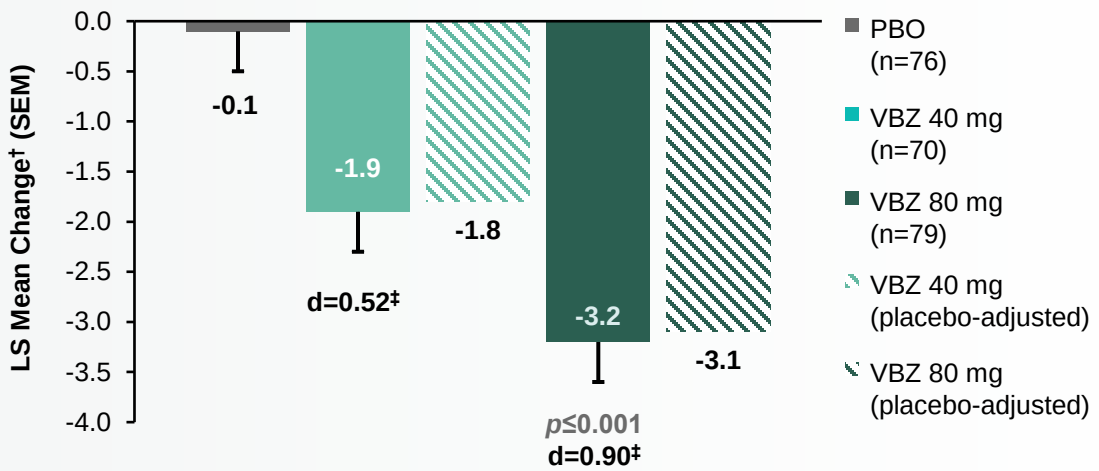
Characteristics (Safety Analysis Set)	PBO (n=76)	VBZ 40 mg (n=72)	VBZ 80 mg (n=79)
Age, mean years (SD)	57 (10.5)	55 (8.5)	56 (10.1)
Age at TD diagnosis, mean years (SD)	49 (10.7)	48 (10.5)	48 (12.5)
Male, n (%)	42 (55.3)	42 (58.3)	39 (49.4)
White, n (%)	43 (56.6)	41 (56.9)	44 (55.7)
Black, n (%)	29 (38.2)	26 (36.1)	32 (40.5)
Schizophrenia/schizoaffective disorder, n (%)	50 (65.8)	48 (66.7)	52 (65.8)
Mood disorder, n (%)*	26 (34.2)	24 (33.3)	27 (34.2)
BPRS score, mean (SD)	29.3 (7.0)	30.6 (7.6)	29.1 (6.6)
AIMS score, mean (SD)	9.9 (4.3)	9.7 (4.1)	10.4 (3.6)
Receiving concomitant antipsychotic medication, n (%)	63 (83)	66 (92)	65 (82)
Receiving concomitant anticholinergic medication, n (%)	22 (28.9)	30 (41.7)	32 (40.5)

Concomitant Medication Use

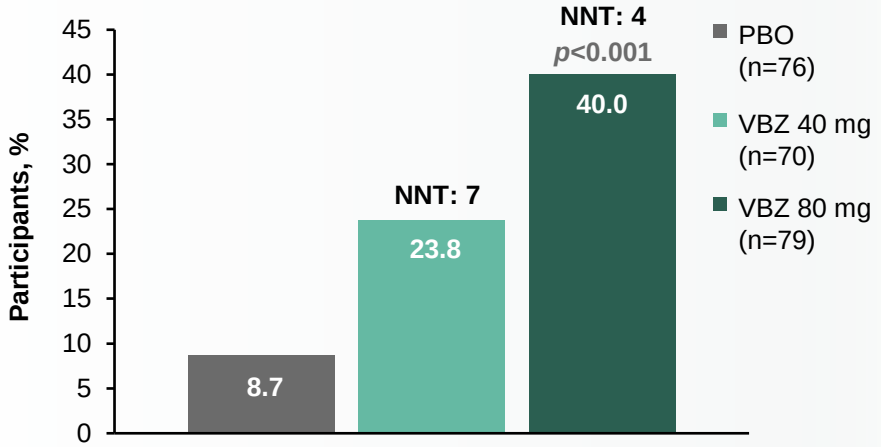
AIMS, Abnormal Involuntary Movement Scale; BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; PBO, placebo; SD, standard deviation; TD, tardive dyskinesia; VBZ, valbenazine.
Data presented for safety analysis set.
*Mood disorder primarily includes BDs and depressive disorders.
1. Hauser RA, et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Data on file. Neurocrine Biosciences, Inc.

KINECT 3: AIMS Results (ITT Population*)

AIMS CFB at Week 6 (Primary Efficacy Endpoint)



Percentage of Participants Who Had ≥50% Improvement in AIMS CFB at Week 6



- AIMS CFB
- Key 2º Endpoint: CGI-TD Score
- Psychiatric Rating Scales CFB

AIMS, Abnormal Involuntary Movement Scale; BL, baseline; CFB, change from baseline; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; ITT, intent-to-treat; MMRM, mixed model repeated measure; NNT, number needed to treat; SEM, standard error of the mean.

*Included all randomized participants who had ≥1 postrandomization AIMS value. †Least squares mean based on the MMRM model, which includes baseline AIMS dyskinesia total score value as a covariate, and treatment group, disease category, visit, treatment group by visit, and baseline by visit interaction as fixed effects, and participant as a random effect. ‡Cohen's d (treatment effect size).

Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.

KINECT 3: TEAEs (Safety Population)

Event, %	Placebo (n=76)	Valbenazine 40 mg (n=72)	Valbenazine 80 mg (n=79)	Valbenazine, Both Dosage Groups (n=151)
Any event	43.4	40.3	50.6	45.7
Any event leading to discontinuation	5.3	5.6	6.3	6.0
Any serious event	3.9	5.6	7.6	6.6
Events by preferred term*				
Somnolence	3.9	5.6	5.1	5.3
Akathisia	1.3	4.2	2.5	3.3
Dry mouth	1.3	6.9	0.0	3.3
Suicidal ideation	5.3	4.2	1.3	2.6
Arthralgia	1.3	1.4	3.8	2.6
Headache	2.6	2.8	2.5	2.6
Vomiting	0.0	0.0	3.8	2.0
Dyskinesia	0.0	0.0	3.8	2.0
Anxiety	0.0	1.4	2.5	2.0
Insomnia	1.3	1.4	2.5	2.0
Fatigue	1.3	2.8	1.3	2.0
Urinary tract infection	3.9	4.2	0.0	2.0
Weight increase	0.0	1.4	2.5	2.0

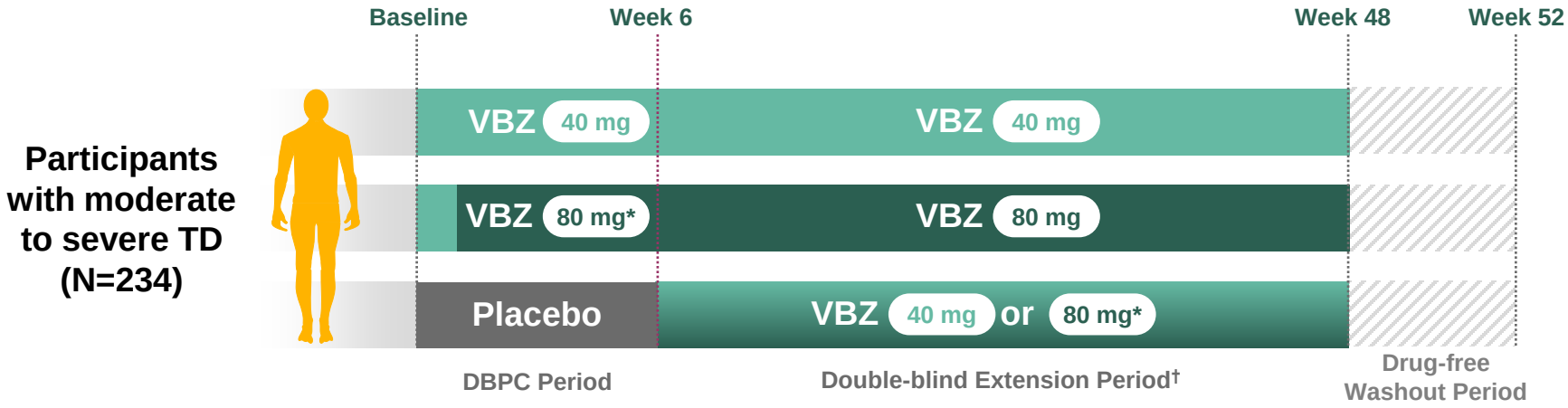
- No observed changes in depression or suicidality safety scales
- No safety signals observed for clinical hematology, chemistry, or ECG

ECG, electrocardiogram; PBO, placebo; TEAE, treatment-emergent adverse event; VBZ, valbenazine.
*Reported in ≥2% of participants in the VBZ total group (both dosage groups).
Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.

KINECT 3 (NCT02274558): Double-blind Extension Period

KINECT 3 Extension: Study Design

42-week extension period of double-blind VBZ treatment



Dosing

- Participants already receiving VBZ continued at the same dose
- Participants who received PBO during the DBPC period were randomized (1:1) to VBZ 40 or 80 mg*

Analysis

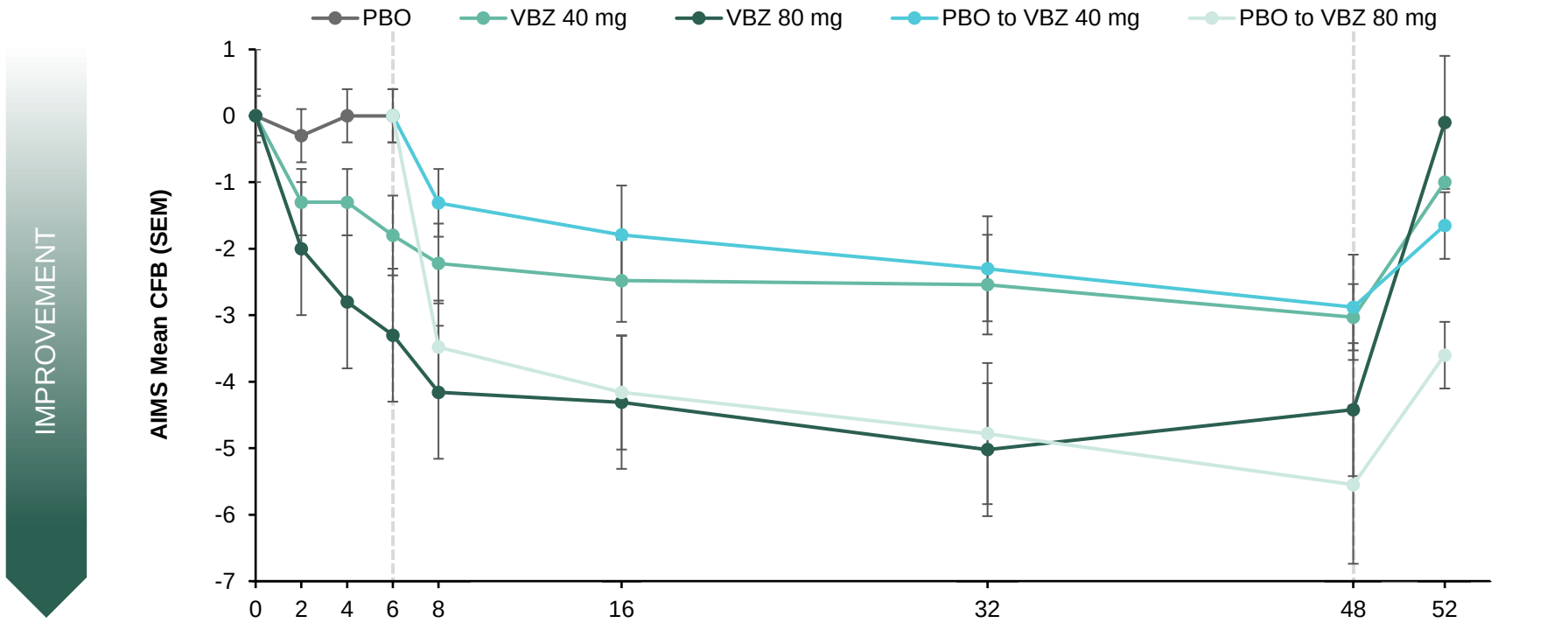
- Efficacy parameters in the VE and washout periods were analyzed descriptively
- No significance testing was conducted between VBZ dose groups

DBPC, double-blind placebo-controlled; TD, tardive dyskinesia; VBZ, valbenazine; VE, valbenazine extension.
*All dosing started at 40 mg and increased to 80 mg after the first week. †Participants and investigators were blinded to treatment arms. Central video reviewers were blinded to study arm and study visit sequence.

Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350.

Participant Disposition

KINECT 3 Extension: AIMS CFB



n value									
PBO	76	76	73	69					
VBZ 40 mg	70	70	64	63	59	50	37	34	34
VBZ 80 mg	79	77	73	70	67	58	50	43	41
PBO to VBZ 40 mg					32	29	27	24	24
PBO to VBZ 80 mg					33	31	27	22	22

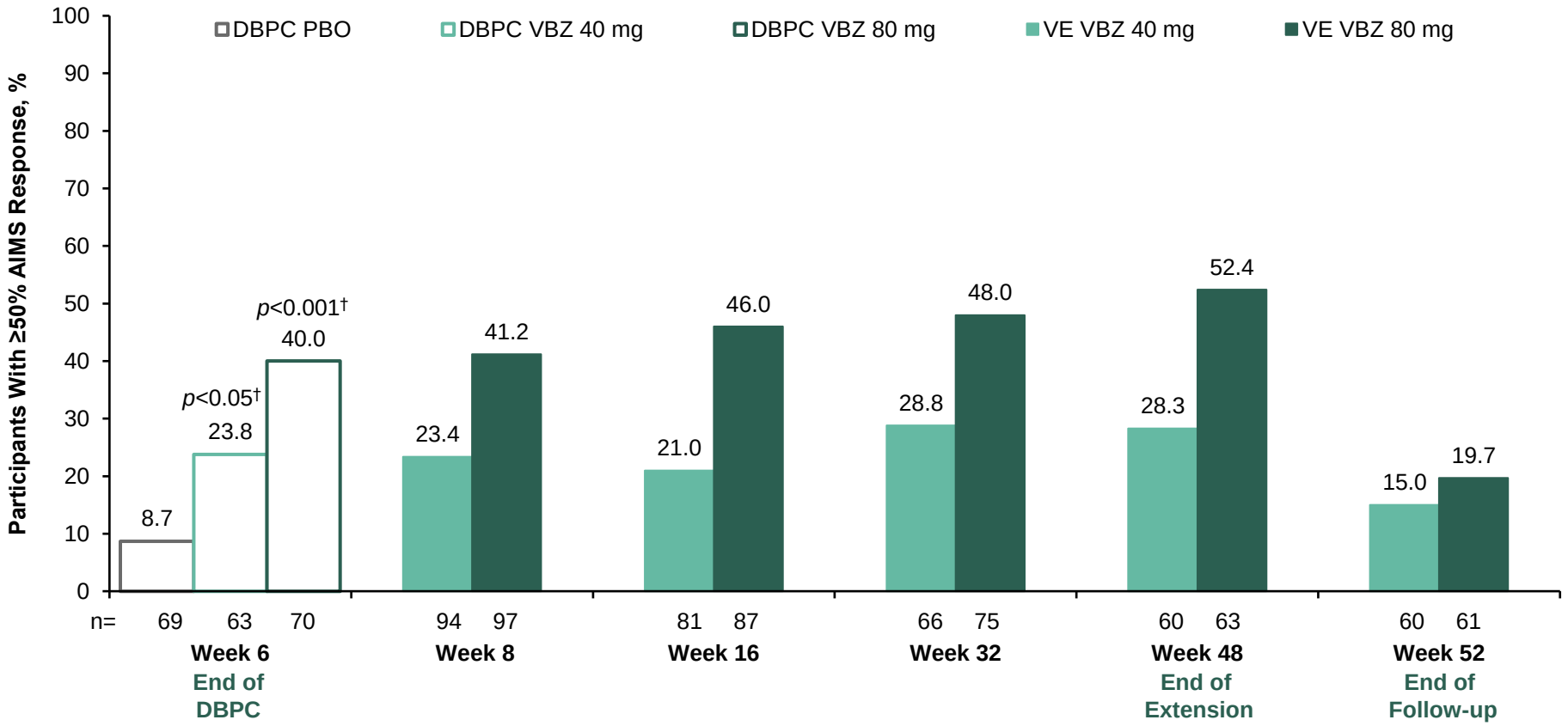
VBZ Groups Only

Rerandomized Groups Only

AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; DBPC, double-blind placebo-controlled; ITT, intent-to-treat; PBO, placebo; SEM, standard error of the mean; VBZ, valbenazine.
Data presented for ITT analysis set.

Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350.

KINECT 3 Extension: ≥50% AIMS Response*

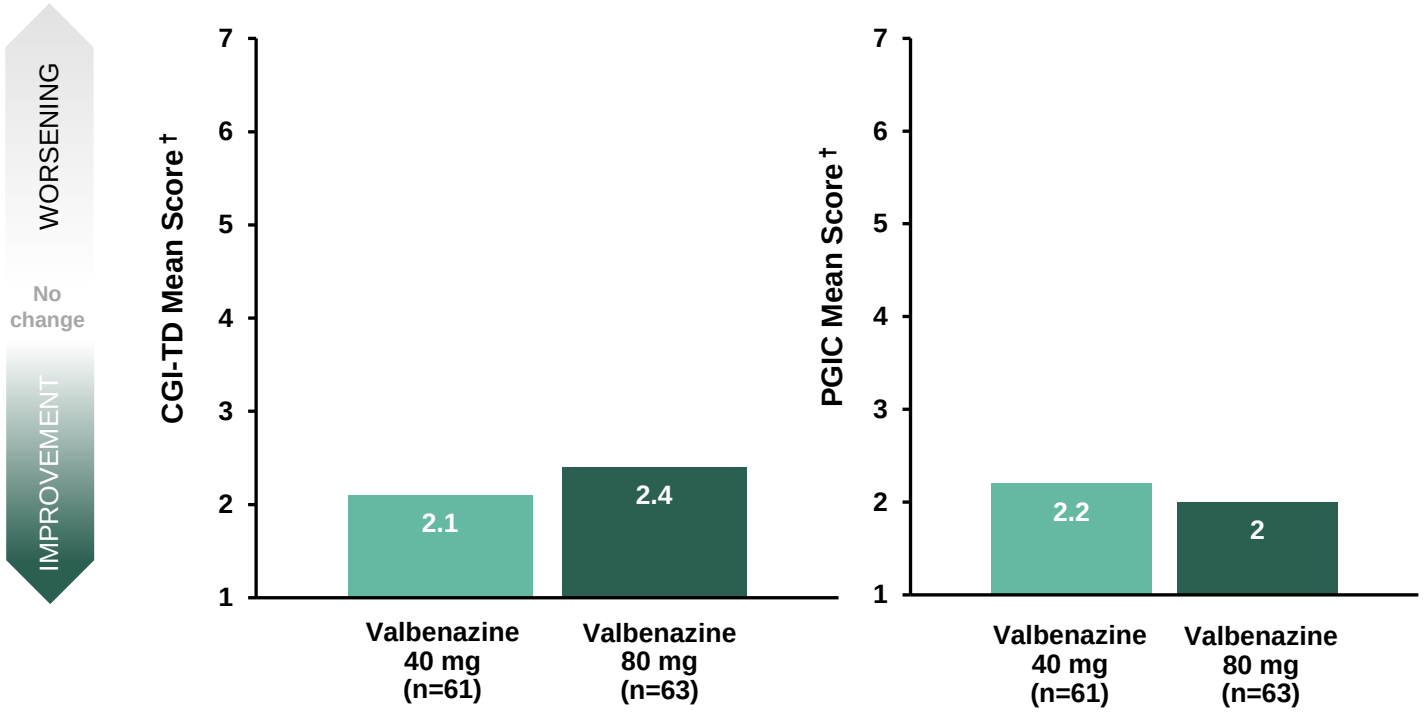


AIMS, Abnormal Involuntary Movement Scale; DBPC, double-blind placebo-controlled; PBO, placebo; VBZ, valbenazine; VE, valbenazine extension.
VE and drug-free follow-up periods: no significance testing between doses were performed.
*AIMS response threshold: participants with ≥50% reduction in AIMS score. †*p*-value versus PBO at end of DBPC, based on a 2-sided Cochran-Mantel-Haenszel analysis.
Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350.

KINECT 3 Extension: CGI-TD and PGIC

Overall, both clinicians and patients reported sustained improvements in TD by the end of valbenazine treatment (48 weeks)

Mean CGI-TD and PGIC Scores at Week 48



- CGI-TD Mean Scores By Study Visit
- CGI-TD Response By Study Visit
- PGIC Response By Study Visit

†Total change in condition rated as 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.
CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change; TD, tardive dyskinesia; VBZ, valbenazine.

Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350.

KINECT 3 Extension: Adverse Events[1,2]

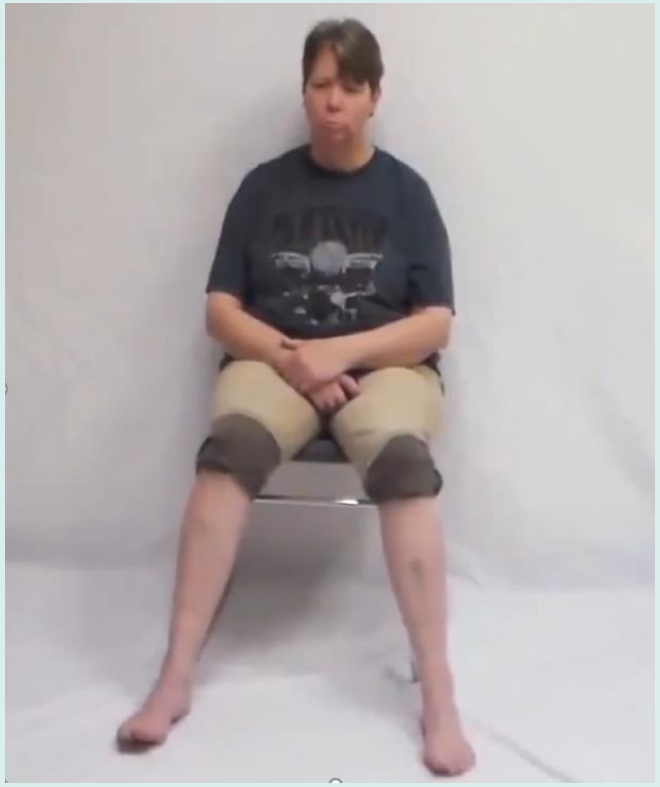
AEs Reported in ≥4%	Valbenazine 40 mg (n=97)	Valbenazine 80 mg (n=101)
Any AE, %	62	76
Diarrhea	3	8
Dizziness	4	7
Headache	7	7
Urinary tract infection	6	7
Suicidal ideation	5	5
Bronchitis	2	4
Constipation	4	4
Cough	3	4
Nasal congestion	1	4
Nausea	3	4
Somnolence	3	4
Weight increase	1	4
Anxiety	4	3
Decreased appetite	4	3
Vomiting	4	3
Weight decreased	4	3
Depression	6	2

AE, adverse event; VBZ, valbenazine.

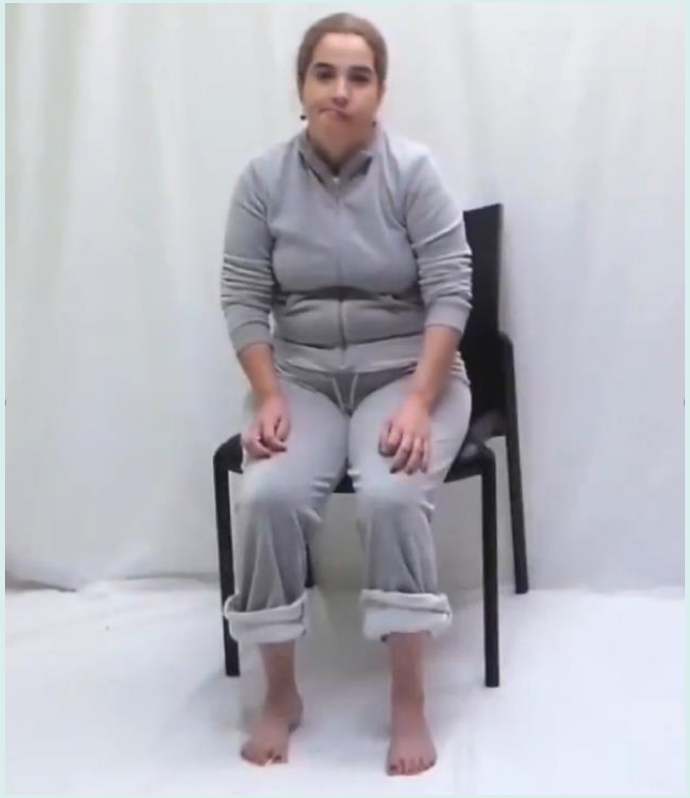
1. Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350. 2. Data on file. Neurocrine Biosciences, Inc.

KINECT 3 Patient Cases

Case 1: 54-Year-Old White Female With Mood Disorder (Bipolar 1)



Case 2: 44-Year-Old Hispanic Female With Mood Disorder (Major Depression)

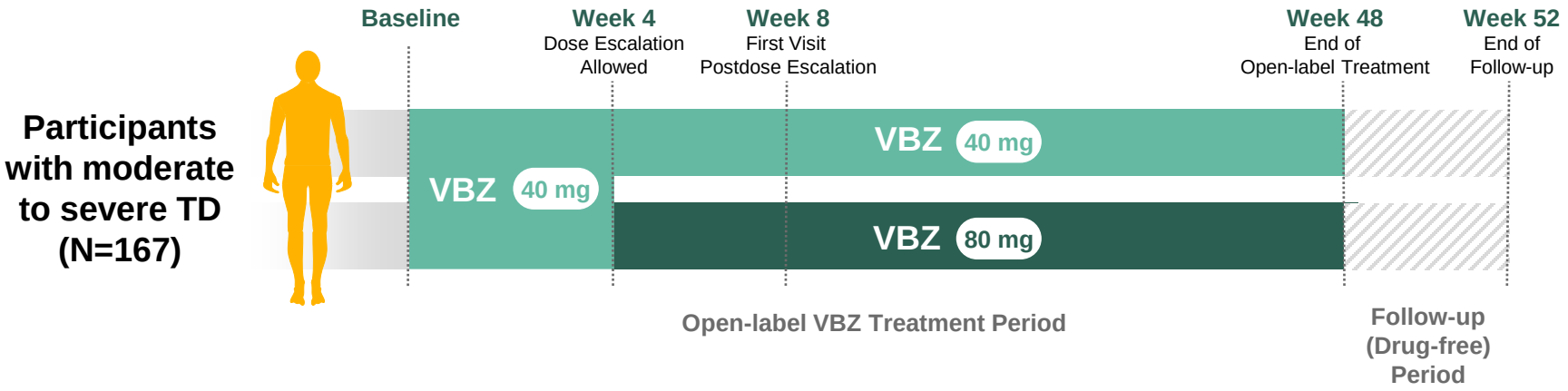


Patients have consented to Neurocrine's use of these videos and their protected health information.

KINECT 4 (NCT02405091): Long-term, Open-label Study

KINECT 4: Study Design

Open-label study to evaluate safety and tolerability of once-daily VBZ



Dosing

- All participants received VBZ 40 mg for 4 weeks
- At the end of Week 4, dose could be escalated to 80 mg if:
  - CGI-TD was ≥3*
  - 40 mg was tolerated
- Participants unable to tolerate 80 mg were allowed a dose reduction to 40 mg between Weeks 4–48
- Participants unable to tolerate 40 mg were discontinued from the study

CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; TD, tardive dyskinesia; VBZ, valbenazine.
Postbaseline study visits during open-label treatment were at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
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; 80→40 mg: dose reduction from 80 to 40 mg.
Patients who received 80 mg in the KINECT 4 study followed a different dosing schedule than those in the KINECT 3 pivotal study. In KINECT 3, patients had a dose increase from 40 to 80 mg after Week 1. In KINECT 4, patients had a dose increase from 40 to 80 mg after Week 4. The impact of this on long-term effectiveness is not known.
*Including CGI-TD scores ranging from 3 (“minimally improved”) to 7 (“very much worse”).
Marder SR, et al. ACNP 2017; Palm Springs, CA.

KINECT 4: Eligibility Criteria

Key inclusion criteria

- DSM diagnosis of drug-induced TD for >3 months before screening
- DSM diagnosis of schizophrenia/schizoaffective disorder or mood disorder
- Moderate or severe TD as qualitatively assessed by a blinded, external reviewer based on AIMS videos

Key exclusion criteria

- Comorbid movement disorder that was more prominent than TD
- Significant risk for suicidal or violent behavior

AIMS, Abnormal Involuntary Movement Scale; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; TD, tardive dyskinesia.

Marder SR, et al. ACNP Congress 2017; Palm Springs, CA.

KINECT 4: Assessments

Efficacy

- AIMS total score (sum of items 1–7) by blinded central video raters
  - Scored at baseline, Weeks 8 and 52
- AIMS total score by site investigators (exploratory measure)
  - Scored at baseline, Weeks 8, 12, 24, 36, 48, and 52
- CGI-TD
- PGIC

Safety

- TEAEs
- Laboratory tests
- Vital sign measurements

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.

Marder SR, et al. *J Clin Psychopharmacol.* 2019;39(6):620-627.

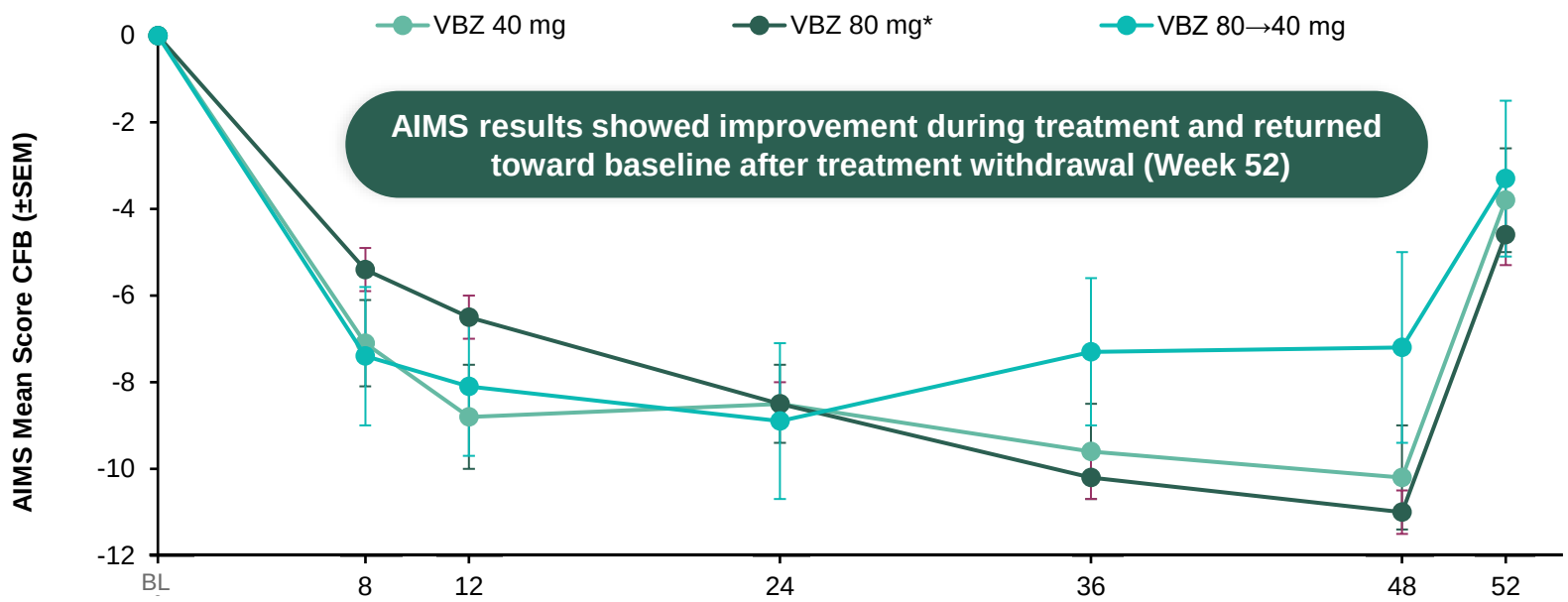
KINECT 4: Baseline Characteristics[1,2]

Characteristic	Valbenazine 40 mg (n=45)	Valbenazine 80 mg (n=107)	All Participants* (n=163)
Age, mean (SD), years	56.8 (11.2)	57.8 (9.0)	57.4 (9.6)
Male, n (%)	21 (46.7)	59 (55.1)	86 (52.8)
Race, n (%)			
White/Caucasian	26 (57.8)	74 (69.2)	110 (67.5)
Black/African American	16 (35.6)	31 (29.0)	48 (29.4)
Other	3 (6.7)	2 (1.9)	5 (3.1)
BMI, mean (SD), kg/m²	27.8 (6.0)	29.0 (5.4)	28.5 (5.5)
Age at TD diagnosis, mean (SD), years	47.8 (11.9)	49.2 (11.4)	48.4 (11.9)
Primary psychiatric diagnosis, n (%)			
Schizophrenia/schizoaffective disorder	37 (82.2)	76 (71.0)	119 (73.0)
Mood disorder	8 (17.8)	31 (29.0)	44 (27.0)
Lifetime suicidal ideation or behavior, n (%)†	17 (37.8)	48 (44.9)	69 (42.3)
AIMS scores, mean (SD)			
Total score by central raters‡	10.2 (3.9)	10.0 (3.9)	10.0 (3.8)
Total score by site raters‡	14.2 (5.5)	15.0 (4.5)	14.6 (4.8)
Item 8 score (severity of abnormal movements overall) by site raters§	3.1 (0.5)	3.2 (0.5)	3.2 (0.6)
Item 9 score (incapacitation due to abnormal movements) by site raters§	2.4 (0.9)	2.6 (0.8)	2.5 (0.9)
Item 10 score (participant's awareness of abnormal movements) by site raters§	2.8 (0.9)	2.7 (0.7)	2.7 (0.8)
Receiving concomitant antipsychotic medication, n (%)	40 (88.9)	95 (88.8)	144 (88.3)
Receiving concomitant anticholinergic medication, n (%)	10 (22.2)	33 (30.8)	44 (27.0)

AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; C-SSRS, Columbia-Suicide Severity Rating Scale; SD, standard deviation; TD, tardive dyskinesia.
*Includes 11 participants who had a dose reduction from 80 mg/day to 40 mg/day after Week 4. †Based on the C-SSRS. ‡Sum of AIMS items 1–7. §AIMS items were scored on a scale from 0 ("none") to 4 ("severe").
1. Marder SR, et al. *J Clin Psychopharmacol.* 2019;39(6):620-627. 2. Data on file. Neurocrine Biosciences, Inc.

KINECT 4: AIMS Mean Score CFB by Visit

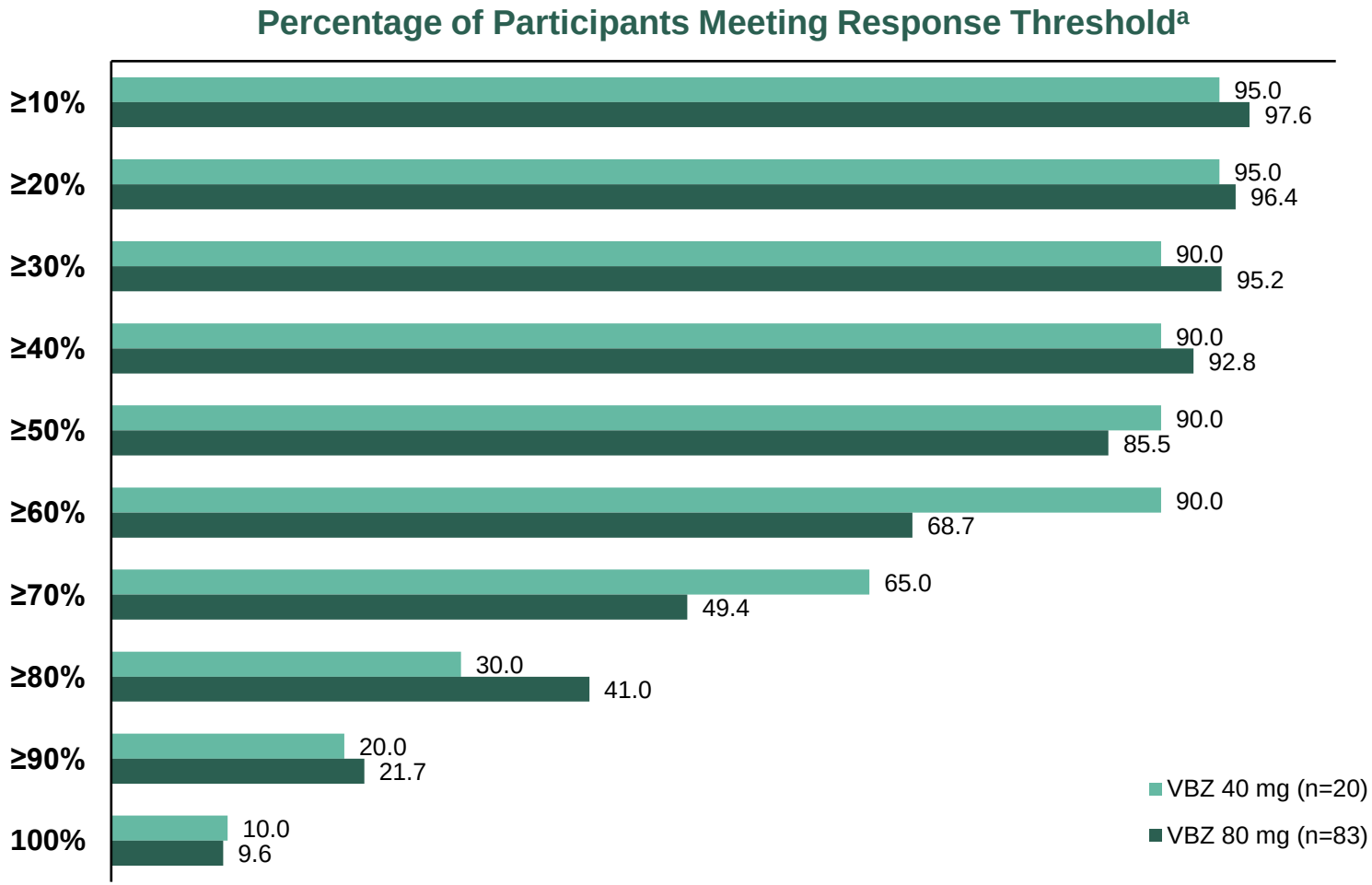
Investigator Raters



40 mg, n	45	33	30	25	20	20	20
80 mg, n	107	105	97	87	79	74	74
80→40 mg, n	11	11	11	10	9	9	9

AIMS, Abnormal Involuntary Movement Scale; BL; baseline; CFB, change from baseline; SEM, standard error of the mean; VBZ, valbenazine.
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; 80→40 mg: dose reduction from 80 to 40 mg.
*Patients who received VBZ 80 mg in the KINECT 4 study followed a different dosing schedule than those in the KINECT 3 pivotal study (dose increase from 40 to 80 mg after Week 4 in KINECT 4 versus after Week 1 in KINECT 3). The impact of this on long-term effectiveness is not known.
Marder SR, et al. *J Clin Psychopharmacol.* 2019;39(6):620-627.

KINECT 4: Response and Shift Analyses, Response Thresholds for AIMS Total Score

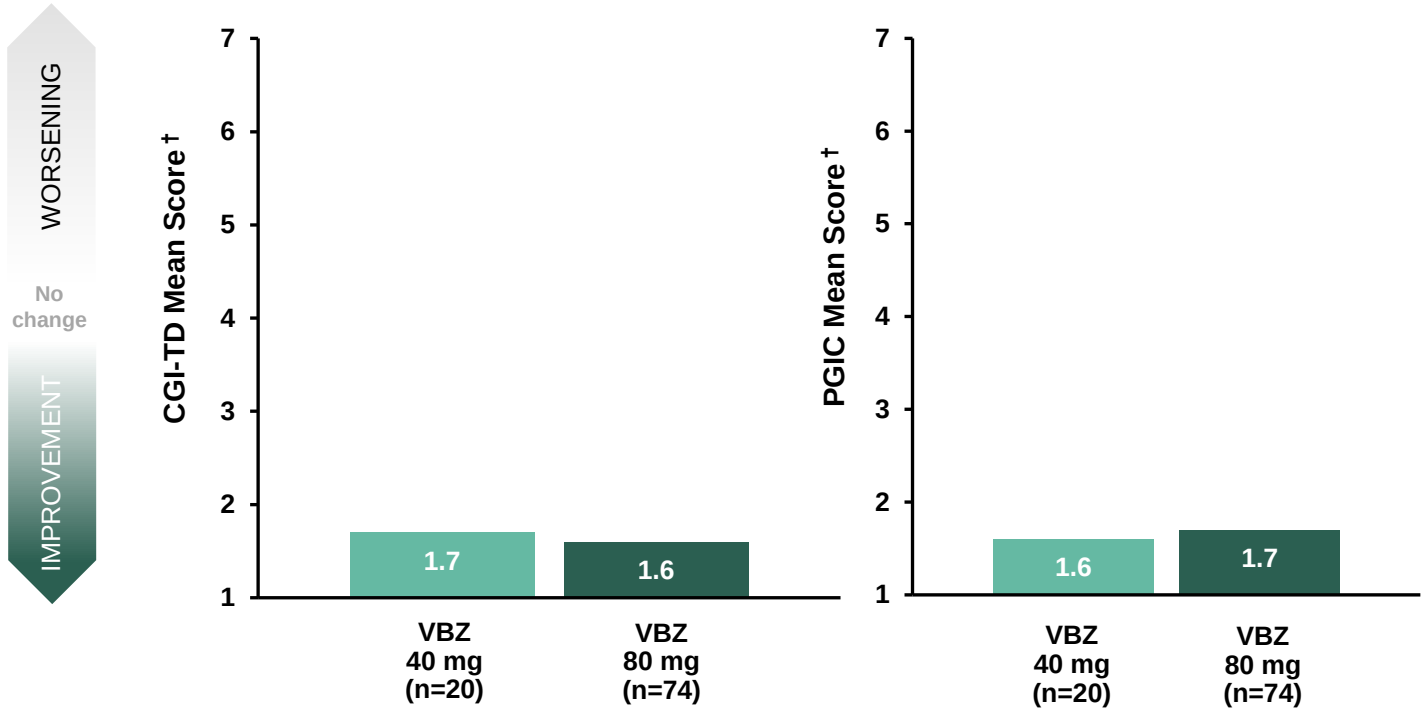


AIMS, Abnormal Involuntary Movement Scale; VBZ, valbenazine.
[a]Includes 9 participants with available data who had a dose reduction from 80 to 40 mg.
Marder SR, et al. NEI 2019; CO Springs, CO.

KINECT 4: CGI-TD and PGIC

Clinician- and patient-rated measures indicated sustained improvements in TD with long-term (up to 48 weeks) valbenazine treatment

Mean CGI-TD and PGIC Scores at Week 48



- CGI-TD Mean Scores By Study Visit
- PGIC Mean Scores By Study Visit
- CGI-TD Response By Study Visit
- PGIC Response By Study Visit

†Total change in condition rated as 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.
Data not shown for 11 participants who had a dose reduction from 80 mg/day to 40 mg/day after week 4.
CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change; TD, tardive dyskinesia; VBZ, valbenazine.

Marder SR, et al. ACNP 2017; Palm Springs, CA.

KINECT 4: Safety and Tolerability

TEAEs*

	VBZ 40 mg (n=35)	VBZ 80 mg (n=107)	VBZ 80→40 mg (n=11)	All Participants (n=153)
Summary, n (%)				
Any TEAE	22 (62.9)	66 (61.7)	11 (100.0)	99 (64.7)
Any serious AE	3 (8.6)	17 (15.9)	1 (9.1)	21 (13.7)
Any TEAE leading to discontinuation	7 (20.0)	11 (10.3)	0 (0.0)	18 (11.8)
TEAEs reported in ≥5% of all participants by preferred term, n (%)				
Urinary tract infection	3 (8.6)	9 (8.4)	1 (9.1)	13 (8.5)
Headache	2 (5.7)	6 (5.6)	0 (0.0)	8 (5.2)

- CFB in vital signs, ECG, and laboratory test were generally small and not clinically significant
- VBZ was generally well-tolerated, and no unexpected safety signals were found

AE, adverse event; CFB, change from baseline; ECG, electrocardiogram; TEAE, treatment-emergent adverse event; VBZ, valbenazine.
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; 80→40 mg: dose reduction from 80 to 40 mg.
1 death was due to breast cancer, which was determined not to be related to the study drug.
*In participants who received ≥1 dose of study drug, reported after Weeks 4 to 48.
Marder SR, et al. *J Clin Psychopharmacol.* 2019;39(6):620-627.

Valbenazine in Tardive Dyskinesia

TD is defined as abnormal, **involuntary movements of the tongue, jaw, trunk, or extremities** that develop in association with medications that block post-synaptic dopamine receptors[1]

A leading theory of the mechanism of TD is the upregulation and subsequent **hypersensitivity of brain dopamine D2 receptors** following prolonged exposure to DRBAs[2]

The 2020 APA Schizophrenia Guidelines recommends reversible VMAT2 inhibitors in patients with **moderate to severe or disabling TD**[3]

VMAT2 inhibitors can also be considered for patients with **mild TD based on factors such as patient preference, associated impairment, or effect on psychosocial functioning**

Valbenazine is a **VMAT2 inhibitor FDA-approved** as safe and effective for the treatment of adults with tardive dyskinesia[4]

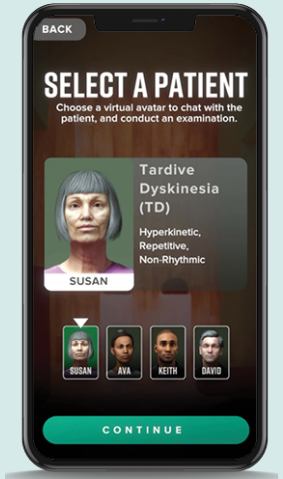
TD, tardive dyskinesia; DRBA, dopamine receptor blocking agent; VMAT2, vesicular monoamine transporter 2; APA, American Psychiatric Association.

1. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. American Psychiatric Association: Washington, DC; 2013. 2. Klawans H, et al. *Acta Neurol Scand*. 1970;46:409-441. 3. APA Practice Guideline for Treatment of Patients with Schizophrenia. Accessed on November 17, 2022. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. 4. INGREZZA® (valbenazine) [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

FREE EDUCATIONAL RESOURCES on Tardive Dyskinesia and Other Drug-Induced Movement Disorders

These educational resources were sponsored and developed by Neurocrine Biosciences, Inc.

Discover TD®



Discover TD® is an interactive experience designed to inform health care providers about tardive dyskinesia and other drug-induced movement disorders. By interacting with hypothetical virtual patients, you can diagnose and determine an appropriate management plan.[a]

[a]For educational purposes only. Should not be interpreted as medical advice for any particular patient. Individual results may vary.

Experience Discover TD®

mind-td.com/discover-td

DIMD Course

The **DIMD Course** is a free, virtual learning resource for health care providers that delves into various clinical aspects of the most common DRBA-induced movement disorders.

Join the DIMD Course

dimdcourse.getlearnworlds.com

Neurocrine Medical Website

The **Neurocrine Medical Website** houses a variety of resources, such as educational podcasts and videos, to assist healthcare providers in the recognition and appropriate differentiation of DRBA-induced movement disorders.

Visit the Neurocrine Medical Website

neurocrinemedical.com

DIMD, drug-induced movement disorder; DRBA, dopamine receptor-blocking agent; TD, tardive dyskinesia.

MED-CON-TD-US-0101

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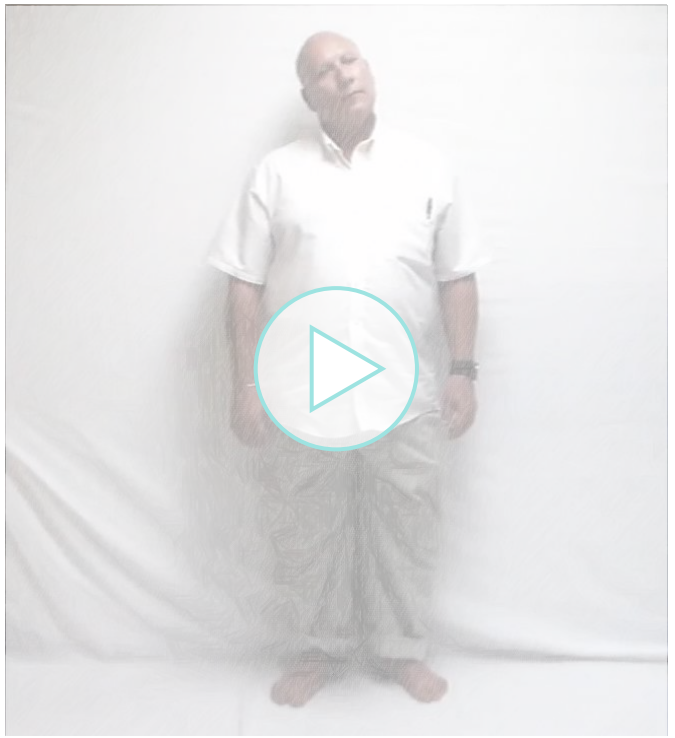
Appendix

Moderate Cervical and Jaw

Open Mouth and Tongue

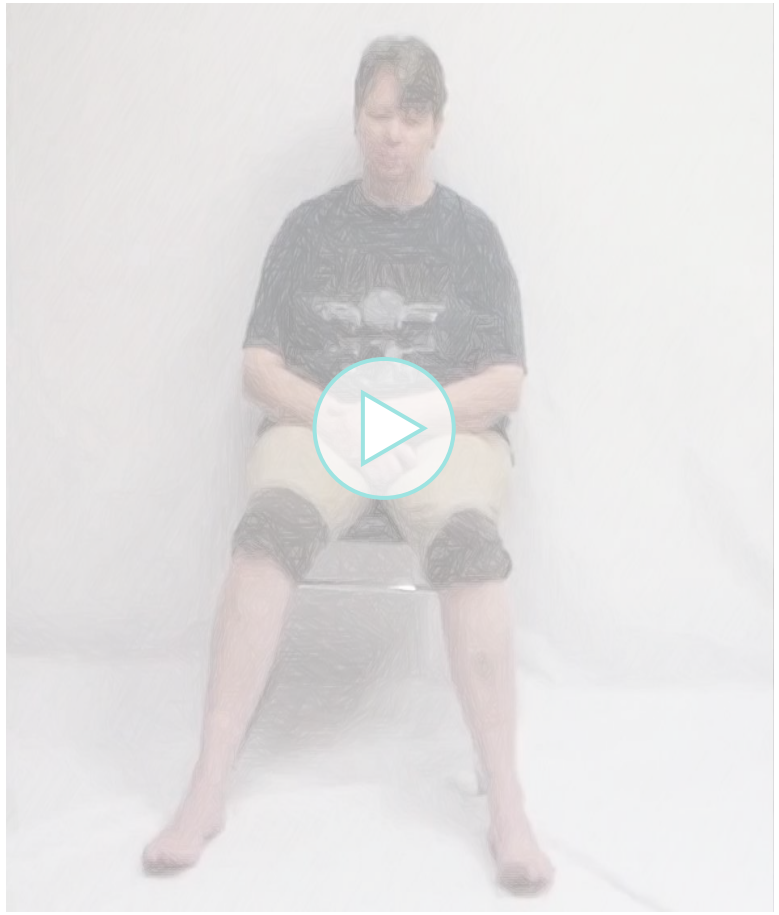
Neck, Shoulder, and Hands (Standing and Walking)



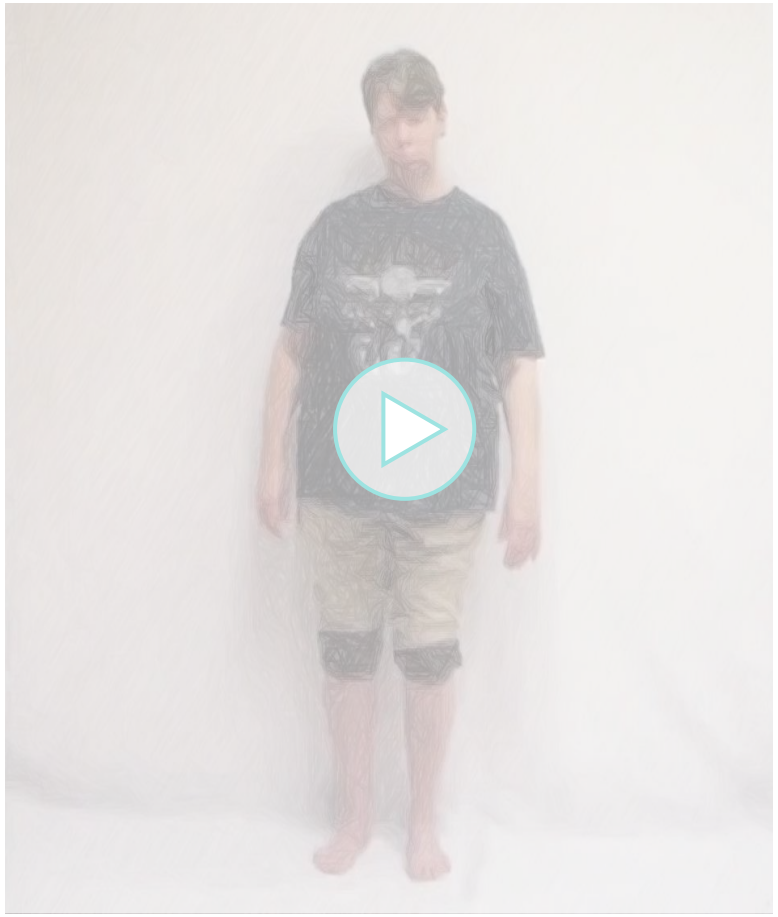
Patients have consented to Neurocrine's use of this video and their protected health information.

Oral-Buccal-Lingual and Legs

Sitting

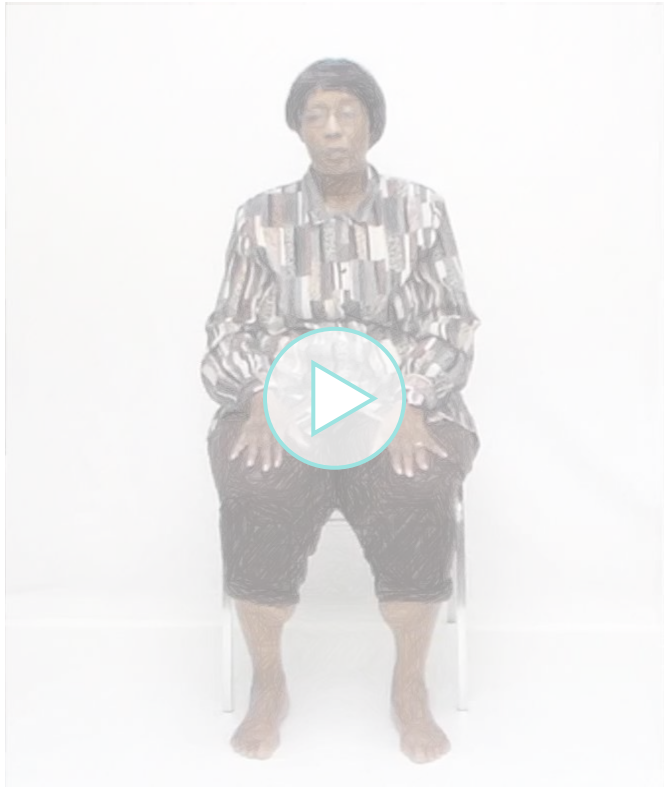


Standing

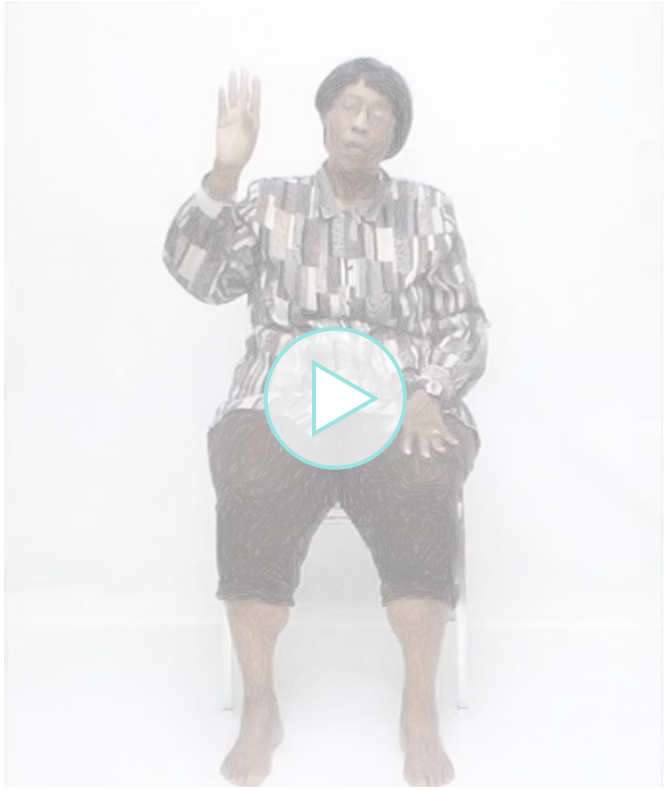


Patients have consented to Neurocrine's use of this video and their protected health information.

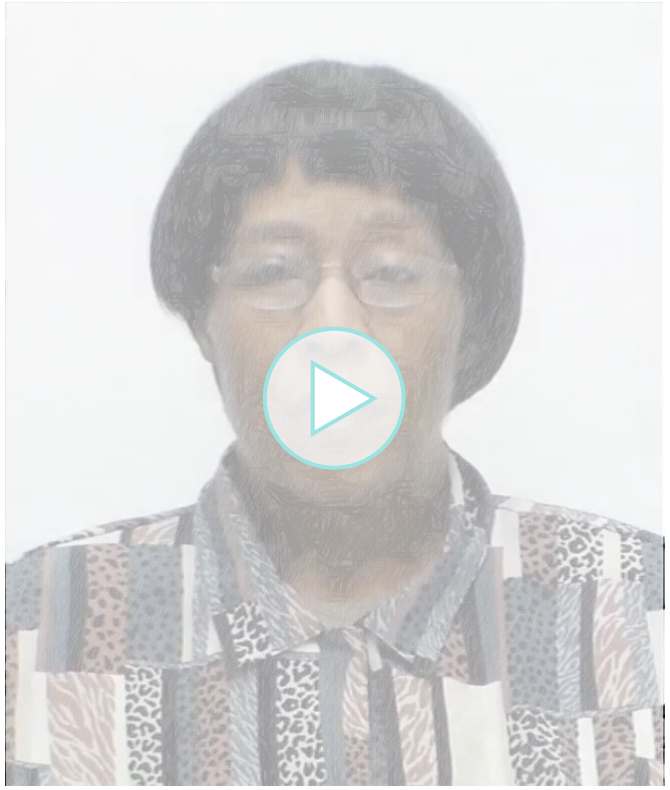
Mild Jaw and Hand



Activation With Hand Movement



Increased Blinking and Jaw Activation



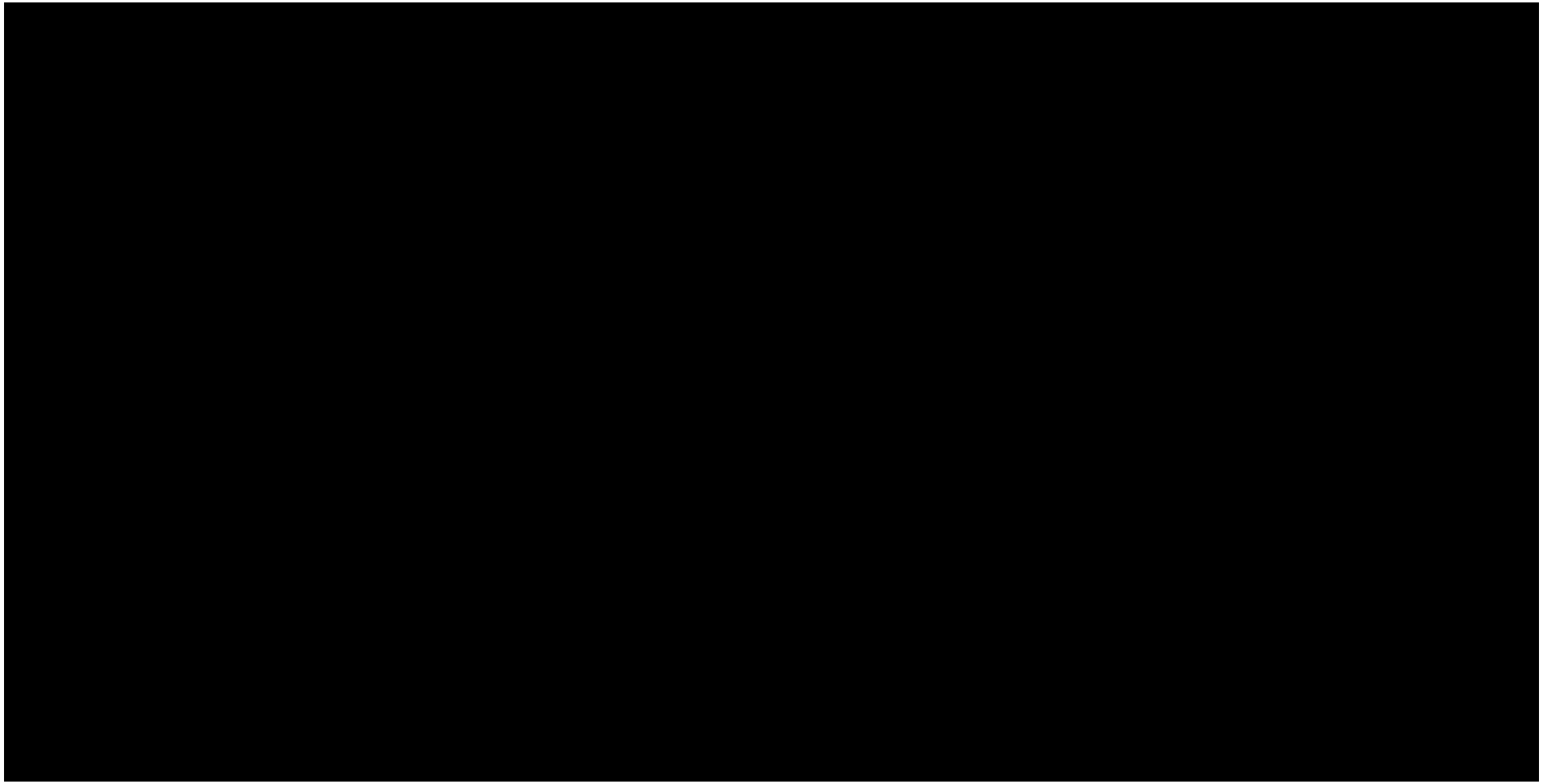
Patients have consented to Neurocrine's use of this video and their protected health information.

Leg and Shoulder Dyskinesia

Facial Grimacing and Head Nodding

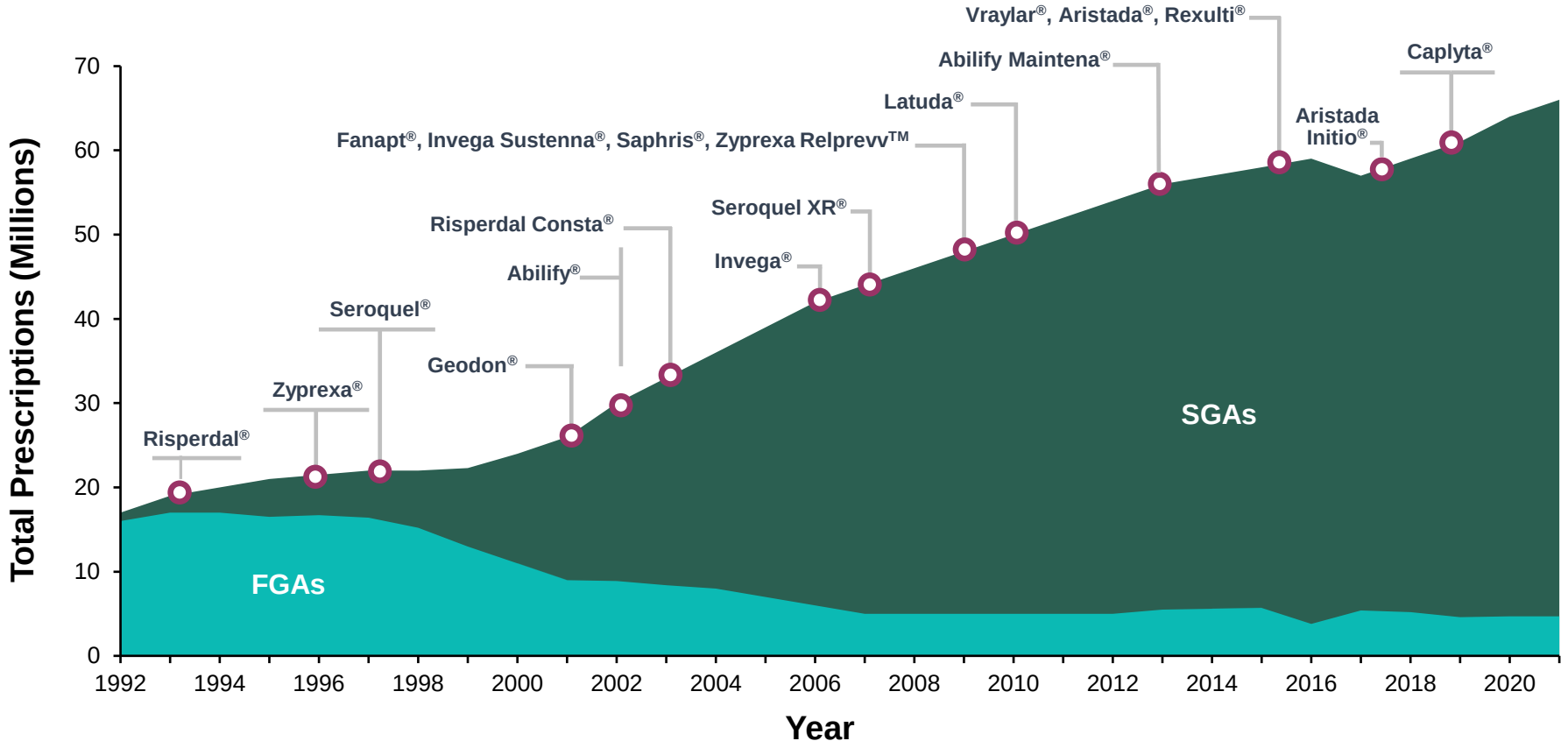
Patients have consented to Neurocrine's use of this video and their protected health information.

Tardive Dyskinesia: Mechanism of Disease Video



TD, tardive dyskinesia.

Trend in Antipsychotic Prescribing



- >4-fold increase in antipsychotic use >25 years[1]
- Use of SGAs in new conditions and client populations has grown over the past 3 decades[1,2]

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

1. Data on file (VBZ-TD-0014). Neurocrine Biosciences, Inc. 2. Alexander GC, et al. *Pharmacoepidemiol Drug Saf*. 2011;20(2)177-184.

Factors Associated With Increased Risk for TD

Risk Factors for TD

Treatment Factors	Patient Factors
Cumulative exposure to antipsychotics[1]	Increased age[1]
Treatment with anticholinergics[1]	Substance abuse[1]
History of EPS[1]	Diagnosis of mood disorder[3,4]
Potency of DRBA[2]	Postmenopausal women[5]
Neuroleptic withdrawal-emergent dyskinesia[6]	

DRBA, dopamine receptor–blocking agent; EPS, extrapyramidal symptoms; TD, tardive dyskinesia.

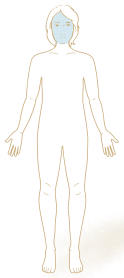
1. Miller DD, et al. *Schizophr Res*. 2005;80:33-43. 2. Divac N. *Biomed Res Int.* 2014;2014:656370. 3. Jeste DV, et al. *Schizophr Bull*. 1993;19:303-315. 4. Mukherjee S. *Arch Gen Psychiatry.* 1986;43:342-346. 5. Seeman MV. *Compr Psychiatry*. 1983;24(2):125-128. 6. Solmi M, et al. *J Neurol Sci*. 2018;389:21-27.

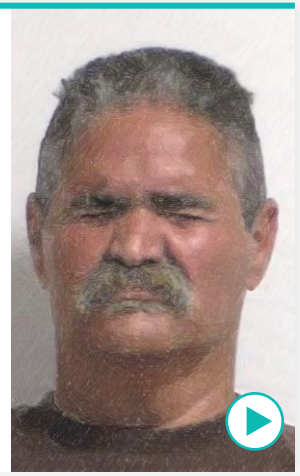
Scoring AIMS (cont'd)

Each total AIMS score can represent a range of clinical presentations

Scores of 4
(1 AIMS item)

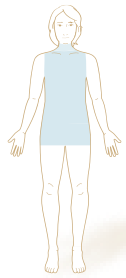
Facial Region





Scores of 4
(1 AIMS item)

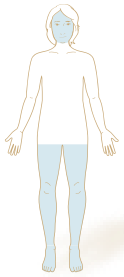
Trunk



Scores of 2
(multiple AIMS items)

Lips

Lower Extremities

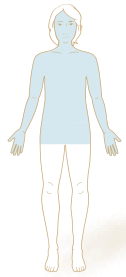


Scores of 1
(4 AIMS items)

Facial Region

Lips **Trunk/Neck**

Upper Extremities



AIMS, Abnormal Involuntary Movement Scale.

Guy W. *ECDEU Assessment Manual for Psychopharmacology*: Revised (DHEW publication number ADM 76-338). National Institute of Mental Health, Psychopharmacology Research Branch; 1976:534-537.

Patients have consented to Neurocrine's use of these videos and their protected health information.

Score of 4
(1 AIMS item)

Facial Region

AIMS, Abnormal Involuntary Movement Scale.
Patients have consented to Neurocrine's use of this video and their protected health information.

Score of 4
(1 AIMS item)

Trunk

AIMS, Abnormal Involuntary Movement Scale.
Patients have consented to Neurocrine's use of this video and their protected health information.

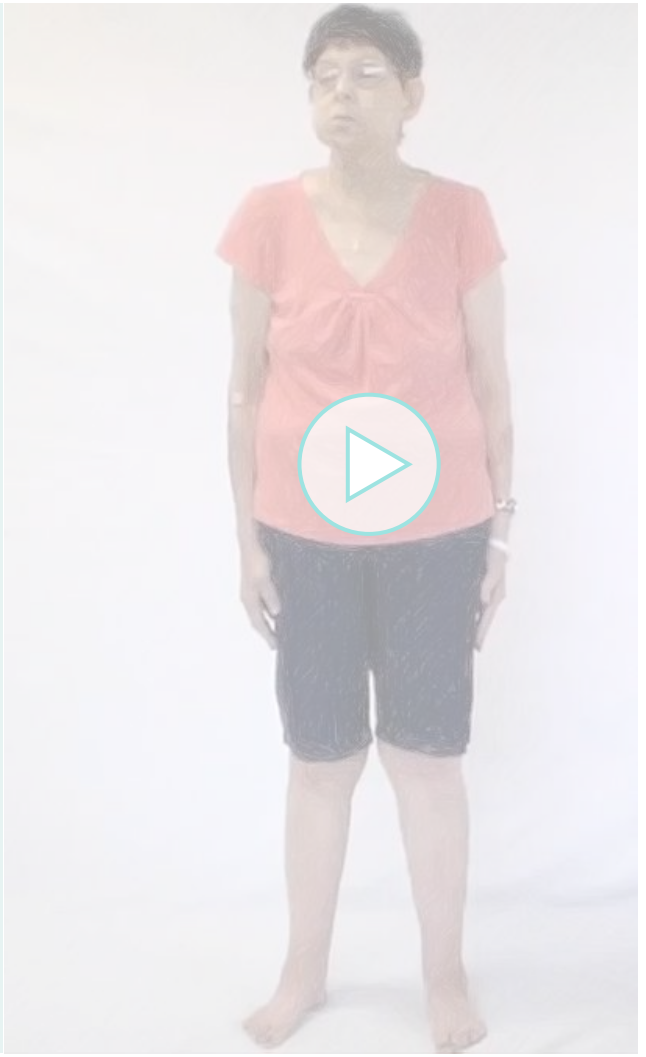
Score of 2
(2 AIMS items)

Lips **Lower Extremities**

AIMS, Abnormal Involuntary Movement Scale.
Patients have consented to Neurocrine's use of this video and their protected health information.

Score of 1
(4 AIMS items)

- Lips
- Facial Region
- Upper Extremities
- Trunk/Neck



AIMS, Abnormal Involuntary Movement Scale.
Patients have consented to Neurocrine's use of this video and their protected health information.

Screen All Patients Taking Antipsychotics at Each Visit

Due to the serious and persistent nature of TD, accurate diagnosis is critical[1]

- Accurate diagnosis may be challenging due to the subtle and often fluctuating symptoms, especially in an older population with various comorbidities
- Misdiagnosis and inappropriate treatment selection can worsen TD[2]
- TD assessments should include regular clinical assessments and periodic assessments using a structured instrument (e.g., AIMS)[1,2]

Clinical Assessments[1,2]

All patients

Baseline → **Every clinical encounter[3]**

Structured Assessments[1]

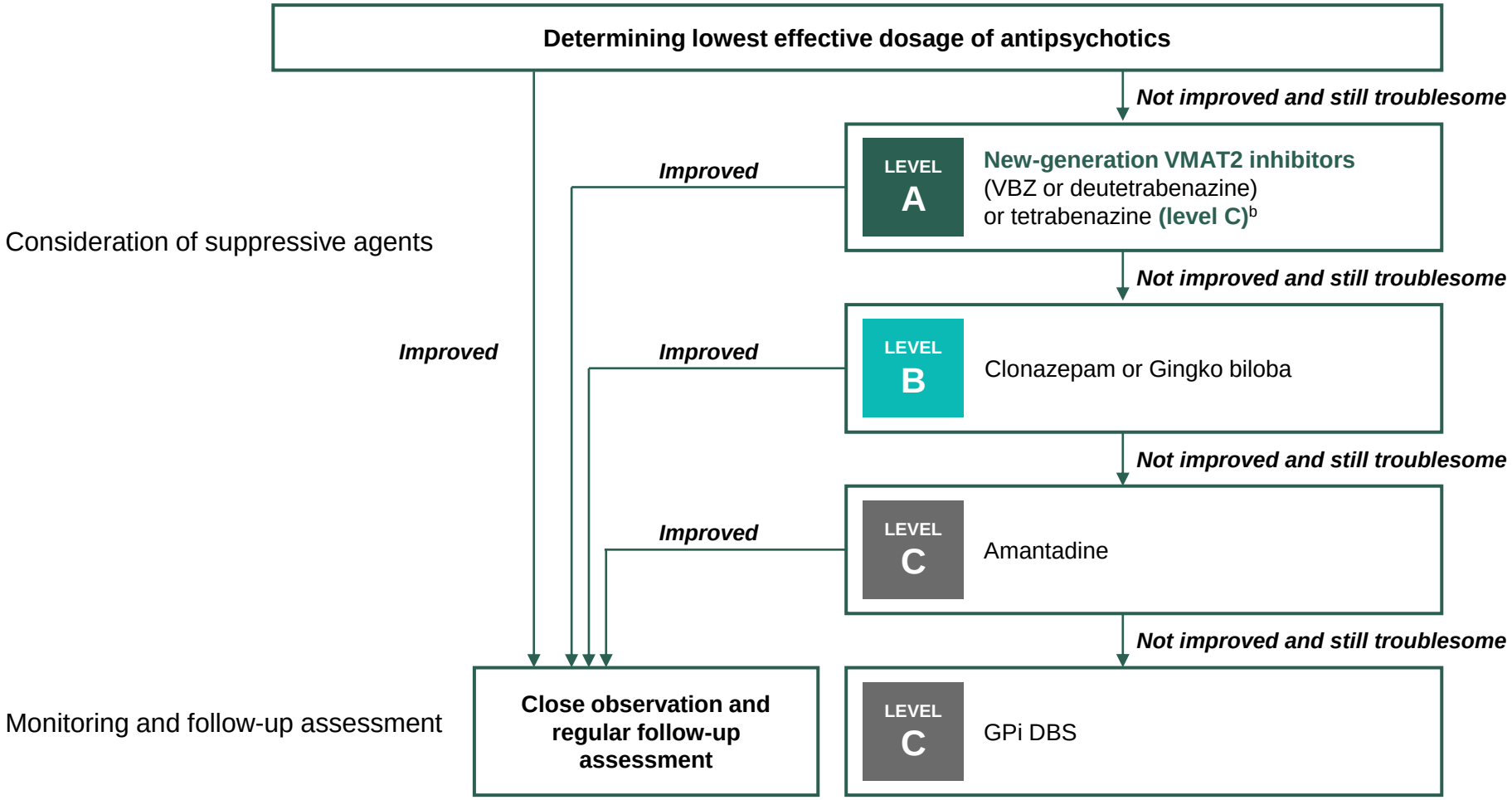
All patients	Higher risk for TD	Lower risk for TD
Baseline	Every 6 months	Every 12 months

If new onset or exacerbation of movements is detected at any visit

CMS, Centers for Medicare & Medicaid Services; TD, tardive dyskinesia; AIMS, Abnormal Involuntary Movement Scale.

1. American Psychiatric Association. Clinical practice guidelines for treatment of patients with schizophrenia. Accessed on March 8, 2023. https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841.
2. Caroff SN, et al. *J Clin Psychiatry.* 2020;81(2):19cs12983. 3. CMS. State operations manual. Appendix PP – guidance to surveyors for long term care facilities. Revised February 3, 2023. Accessed March 31, 2023. https://www.cms.gov/medicare/provider-enrollment-and-certification/guidanceforlawsandregulations/downloads/appendix-pp-state-operations-manual.pdf.

2018 Systematic Review: Practical Treatment Algorithm[a]



GPi DBS, pallidus interna deep brain stimulation; TD, tardive dyskinesia; VBZ, valbenazine; VMAT2, vesicular monoamine transporter type 2.
[a]Adapted for the management of troublesome TD in patients receiving an approved antipsychotic treatment as indicated. Assessment of TD is necessary before treatment.
[b]Consider tetrabenazine if the new-generation VMAT2 inhibitors are unavailable.
Bhidayasiri R, et al. *J Neurol Sci.* 2018;389:67-75.

Valbenazine Mechanism of Action Video

MIDD Modeling & Simulation for Valbenazine 60 mg: Methodology

Exposure-Response Model

Exposure + **Response** = **Prediction of 60 mg efficacy through simulation of 1000 clinical trials**

Population PK data from:
- Phase 1 studies in healthy adults
- Phase 1b and Phase 2 studies
- Total: 381 participants

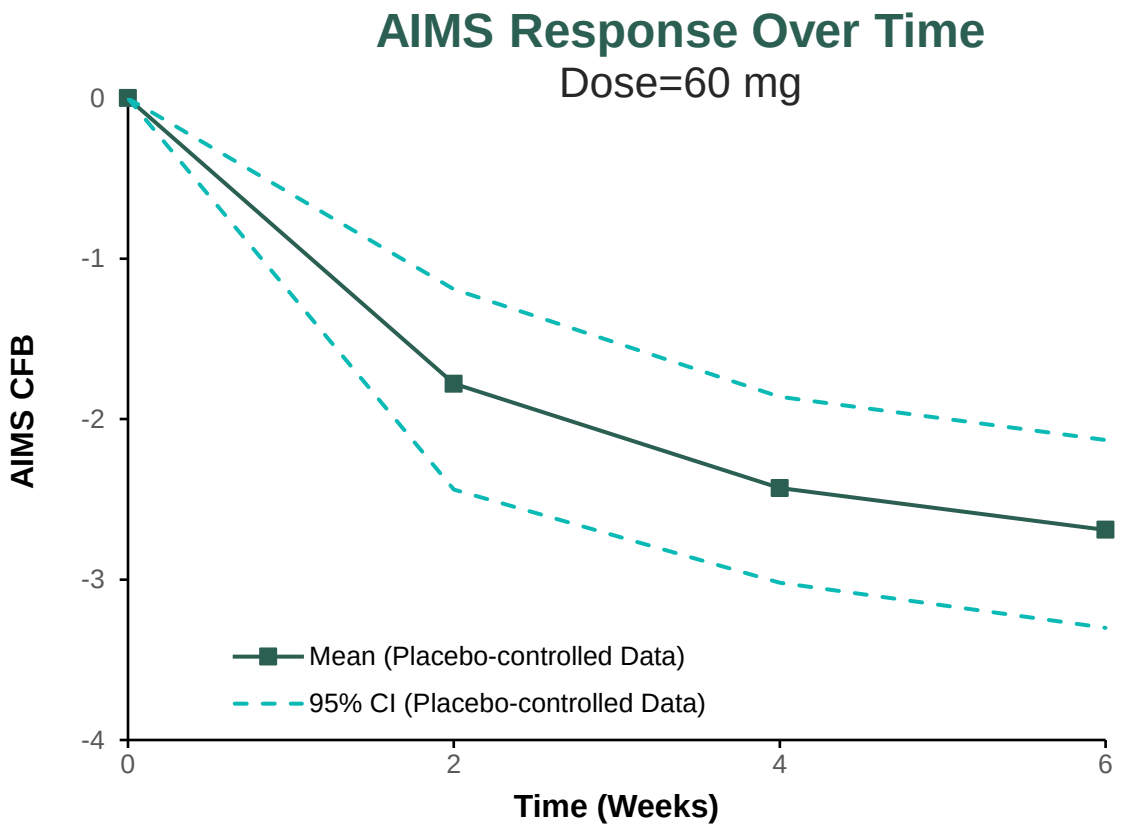
Data from KINECT 3 DBPC Phase (6 weeks)
- 40 and 80 mg
- Total: 235 participants with TD

Simulated clinical trials included:
- 2000 virtual participants
- Participants randomized (1:1:1:1) to PBO, 40, 60, and 80 mg

Continue

MIDD, model-informed drug development; PK, pharmacokinetic; DBPC, double-blind placebo-control; TD, tardive dyskinesia; PBO, placebo.
Data on File. Neurocrine Biosciences, Inc.

MIDD Modeling & Simulation for Valbenazine 60 mg: AIMS Results



Predicted population mean CFB in AIMS at **Week 6** for **valbenazine 60 mg** is

–2.69

(95% CI: –3.30, –2.13)

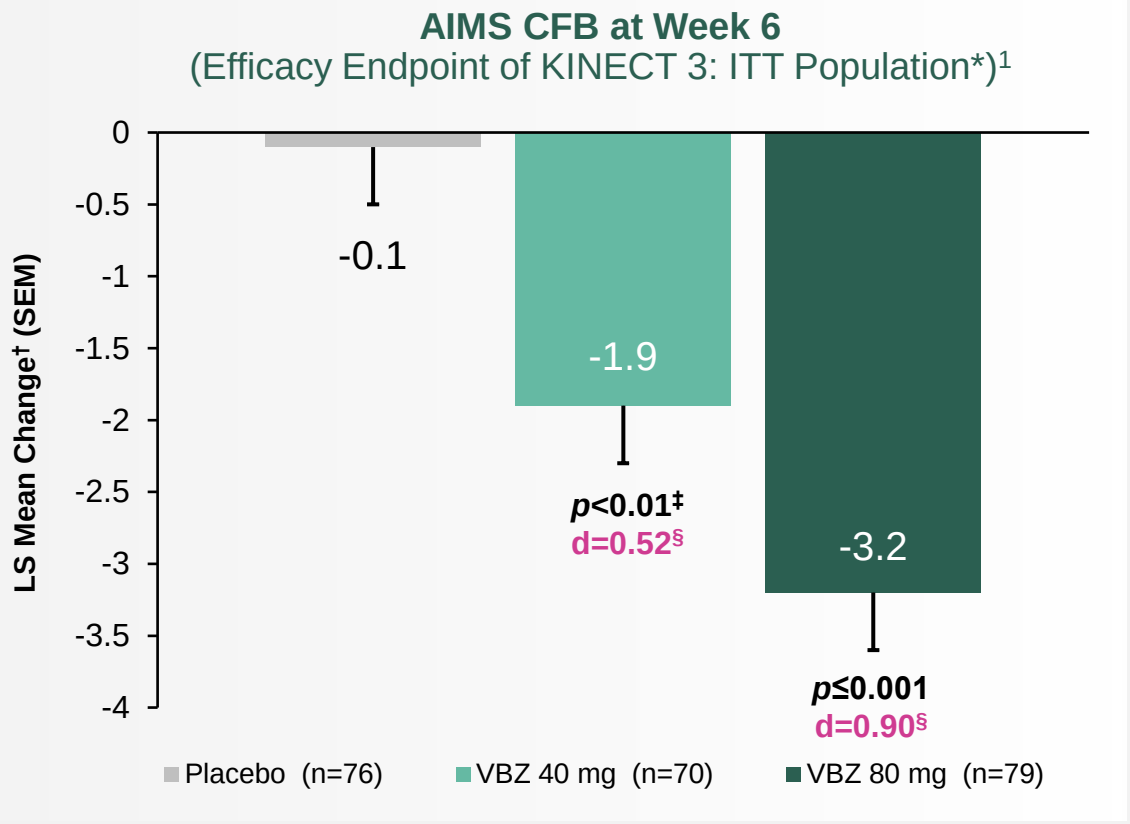
The simulated dataset was designed to replicate the KINECT 3 study methodology, dose regimen, and covariate distributions

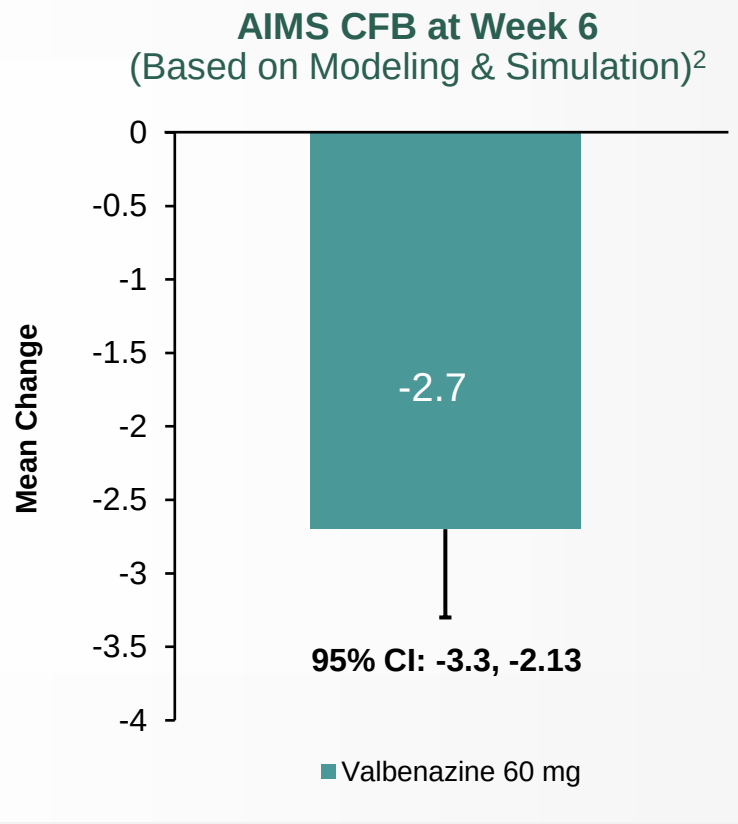
Continue

AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; CI, confidence interval; MIDD, model-informed drug development; AIMS, Abnormal Involuntary Movement Scale.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., 2021.

KINECT 3 & MIDD Modeling & Simulation: AIMS Results





AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LS, least squares; MIDD, model-informed drug development; MMRM, mixed model repeated measure; SEM, standard error of the mean.
*ITT included all randomized participants who had ≥1 postrandomization AIMS value.
†LS mean based on the MMRM model, which includes baseline AIMS dyskinesia total score value as a covariate, and treatment group, disease category, visit, treatment group by visit, and baseline by visit interaction as fixed effects, and participant as a random effect. ‡Nominal p-value, statistical analysis plan-specified hierarchical analysis precluded testing 40-mg result for significance. §Cohen's d (treatment effect size).

1. Hauser RA, et al. *Am J Psych.* 2017;174(5):476-484. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., 2021.

Valbenazine: Drug Interactions

Clinically Significant Drug Interactions with INGREZZA and INGREZZA SPRINKLE

MAOIs	
Clinical impact	Concomitant use of INGREZZA or INGREZZA SPRINKLE with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of INGREZZA or INGREZZA SPRINKLE.
Prevention or management	Avoid concomitant use of INGREZZA or INGREZZA SPRINKLE with MAOIs, or within 14 days of discontinuing therapy with an MAOI.
Examples	Isocarboxazid, phenelzine, selegiline
Strong CYP3A4 Inhibitors	
Clinical impact	Concomitant use of INGREZZA or INGREZZA SPRINKLE with strong CYP3A4 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA or INGREZZA SPRINKLE alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.
Prevention or management	Reduce INGREZZA or INGREZZA SPRINKLE dose when INGREZZA or INGREZZA SPRINKLE is coadministered with a strong CYP3A4 inhibitor.
Examples	Itraconazole, ketoconazole, clarithromycin

Continue

AUC, area under the curve; C_{max}, maximum observed concentration; CYP, cytochrome P450; MAOI, monoamine oxidase inhibitor.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

Valbenazine: Drug Interactions (cont'd)

Clinically Significant Drug Interactions with INGREZZA and INGREZZA SPRINKLE

Strong CYP2D6 Inhibitors	
Clinical impact	Concomitant use of INGREZZA or INGREZZA SPRINKLE with strong CYP2D6 inhibitors increased the exposure (Cmax and AUC) to valbenazine's active metabolite compared with the use of INGREZZA or INGREZZA SPRINKLE alone. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions.
Prevention or management	Reduce INGREZZA or INGREZZA SPRINKLE dose when INGREZZA or INGREZZA SPRINKLE is coadministered with a strong CYP2D6 inhibitor.
Examples	Paroxetine, fluoxetine, quinidine
Strong CYP3A4 Inducers	
Clinical impact	Concomitant use of INGREZZA or INGREZZA SPRINKLE with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA or INGREZZA SPRINKLE alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.
Prevention or management	Concomitant use of strong CYP3A4 inducers with INGREZZA or INGREZZA SPRINKLE is not recommended.
Examples	Rifampin, carbamazepine, phenytoin, St. John's wort*
Digoxin	
Clinical impact	Concomitant use of INGREZZA or INGREZZA SPRINKLE with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp)
Prevention or management	Digoxin concentrations should be monitored when co-administering INGREZZA or INGREZZA SPRINKLE with digoxin. Increased digoxin exposure may increase the risk of exposure-related adverse reactions. Dosage adjustment of digoxin may be necessary.

AUC, area under the curve; C_{max}, maximum observed concentration; CYP, cytochrome P450; P-gp, P-glycoprotein.
*The induction potency of St. John's wort may vary widely based on preparation.
INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., 2021.

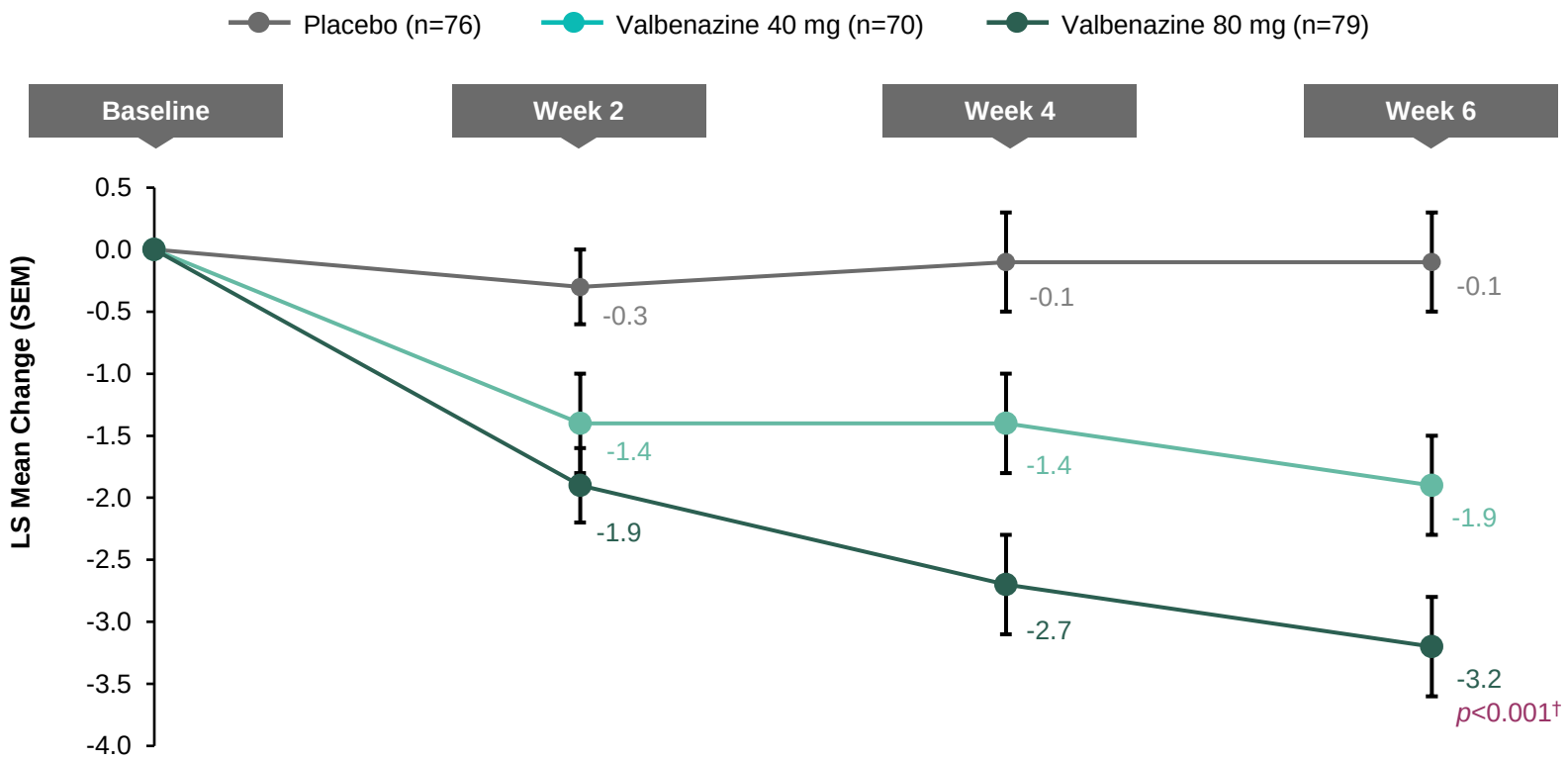
KINECT 3: Concomitant Medication Use (Safety Population)

Medications*	Placebo (n=76)	VBZ 40 mg (n=72)	VBZ 80 mg (n=79)
Typical antipsychotics, n (%)			
Haloperidol	4 (5.3)	13 (18.1)	10 (12.7)
Atypical antipsychotics, n (%)			
Quetiapine	18 (23.7)	23 (31.9)	14 (17.7)
Risperidone	14 (18.4)	11 (15.3)	16 (20.3)
Aripiprazole	10 (13.2)	8 (11.1)	10 (12.7)
Olanzapine	11 (14.5)	8 (11.1)	8 (10.1)
Ziprasidone	1 (1.3)	4 (5.6)	9 (11.4)
Antidepressants, n (%)			
Trazodone	10 (13.2)	17 (23.6)	16 (20.3)
Citalopram	10 (13.2)	10 (13.9)	10 (12.7)
Sertraline	13 (17.1)	9 (12.5)	8 (10.1)
Fluoxetine	10 (13.2)	7 (9.7)	3 (3.8)
Mirtazapine	6 (7.9)	8 (11.1)	5 (6.3)
Anticholinergics, n (%)			
Benztropine	19 (25.0)	29 (40.3)	26 (32.9)

*Taken by ≥10% of participants in any treatment group.
VBZ, valbenazine.
Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.

KINECT 3: AIMS CFB by Study Visit (ITT Population*)[1,2]

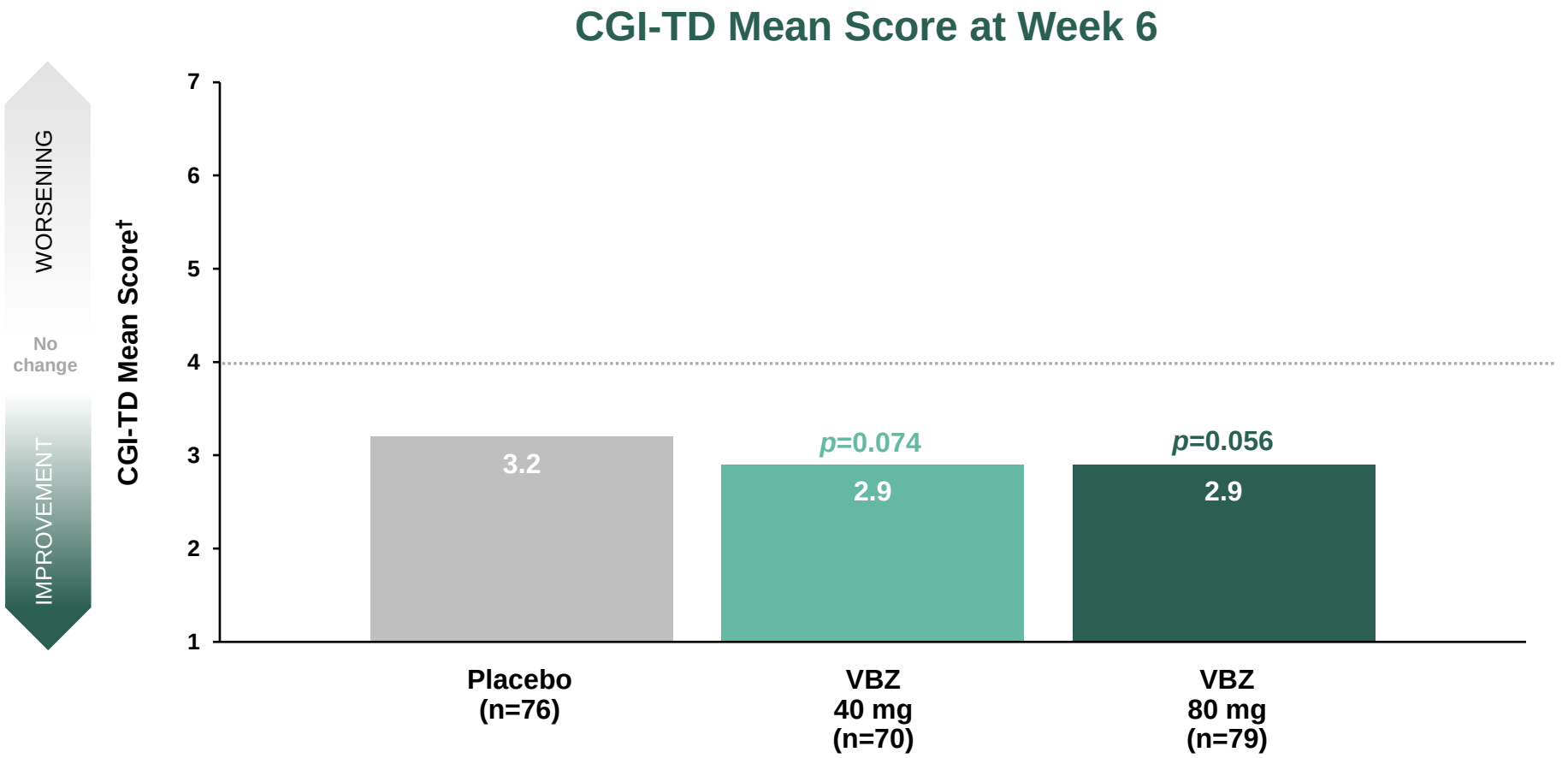
Some participants began to see a response as early as Week 2



n value				
PBO	76	76	73	69
VBZ 40 mg	70	70	64	63
VBZ 80 mg	79	77	73	70

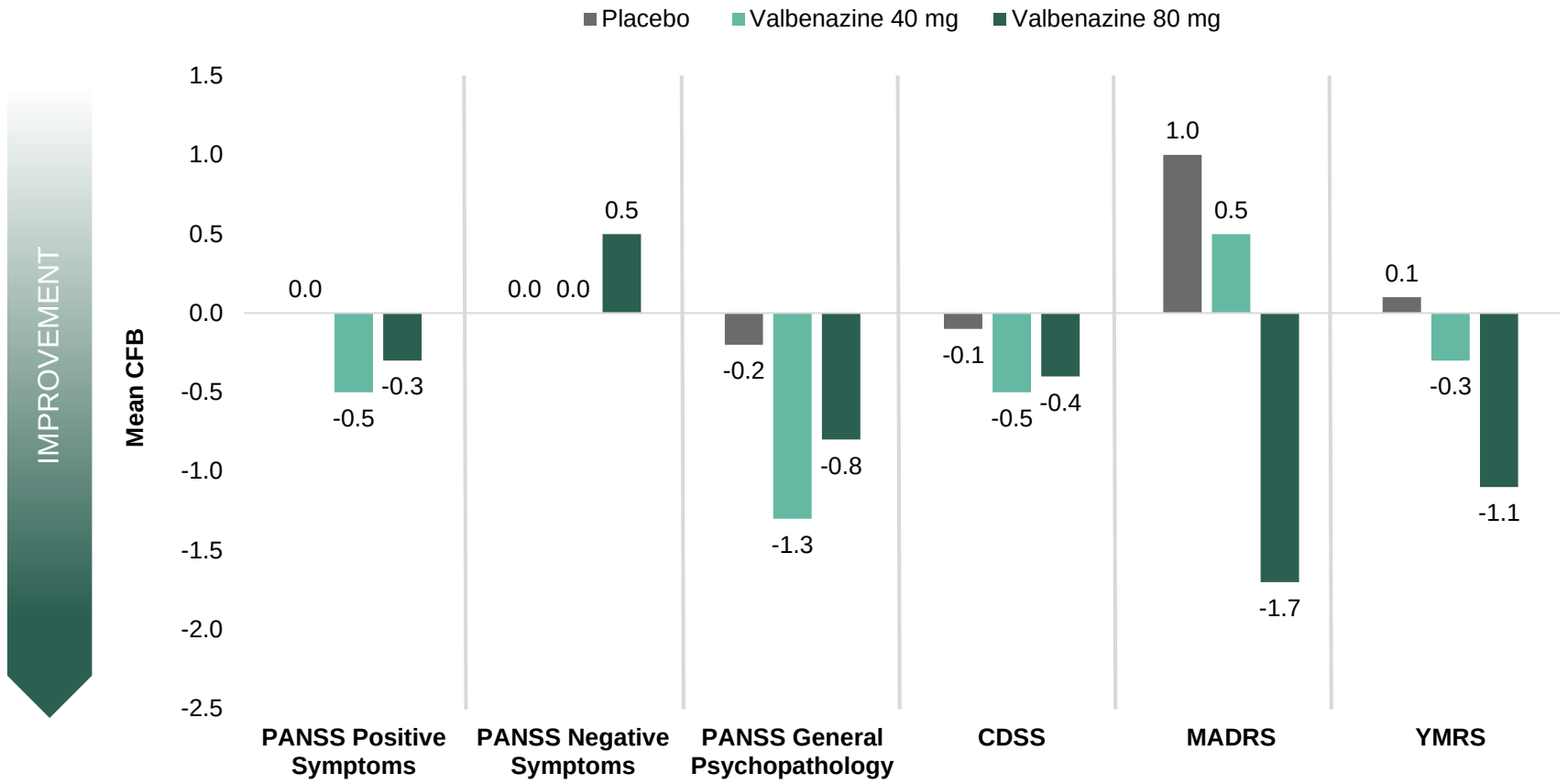
AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; ITT, intent-to-treat; PBO, placebo; VBZ, valbenazine.
*ITT: Included all randomized participants who had ≥1 postrandomization AIMS value. †Dose that was statistically significantly different from placebo after adjusting for multiplicity.
Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.

KINECT 3: Key Secondary Endpoint CGI-TD Score (ITT Population*)



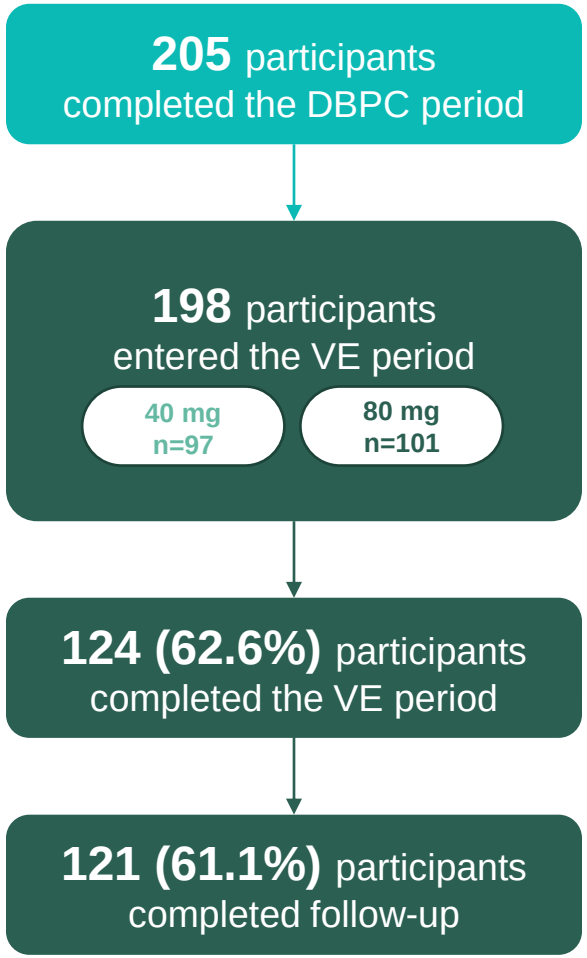
CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; ITT, intent-to-treat; VBZ, valbenazine.
*ITT: Included all randomized participants who had ≥1 postrandomization AIMS value. †Total change in condition rated as 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.
Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.

KINECT 3 Psychiatric Rating Scales: CFB to Week 6



CDSS, Calgary Depression Scale for Schizophrenia; CFB, change from baseline; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; VBZ, valbenazine; YMRS, Young Mania Rating Scale.
For the PANSS and CDSS: placebo n=50, VBZ 40 mg n=48, VBZ 80 mg n=52; MADRS and YMRS: placebo n=26, VBZ 40 mg n=24, VBZ 80 mg n=27.
Factor SA, et al. *MDS* 2016.

KINECT 3 Extension: Participant Disposition



VE safety population included 198 participants

69.2% had ≥1 TEAE

14.6% had ≥1 SAE

Reasons for discontinuation from VE period

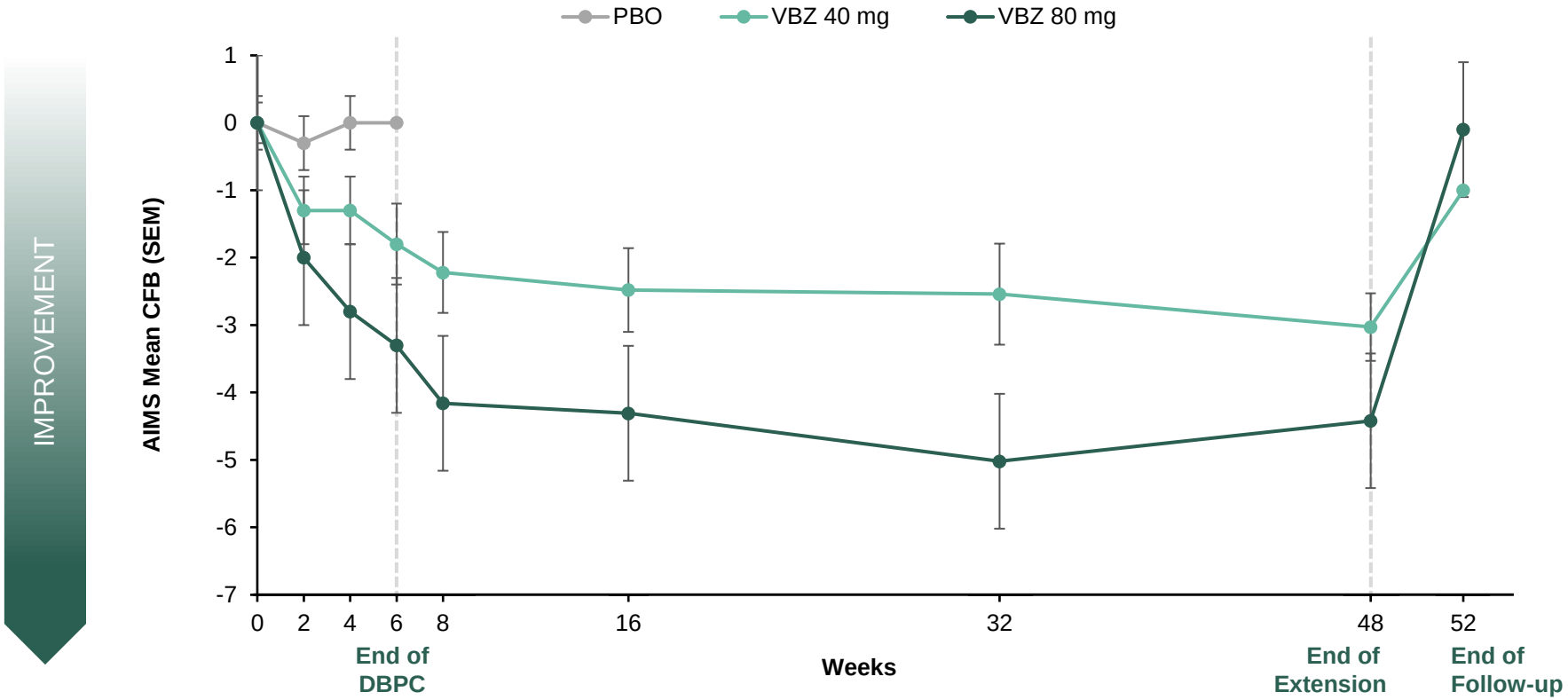
15.7% AEs

8.6% withdrawal of consent

7.1% loss to follow-up

AE, adverse event; DBPC, double-blind placebo-controlled; SAE, serious adverse event; TEAE, treatment-emergent adverse event; VE, valbenazine extension.
Grigoriadis D, et al. ACNP 2016.

KINECT 3 Extension: AIMS CFB for VBZ Groups

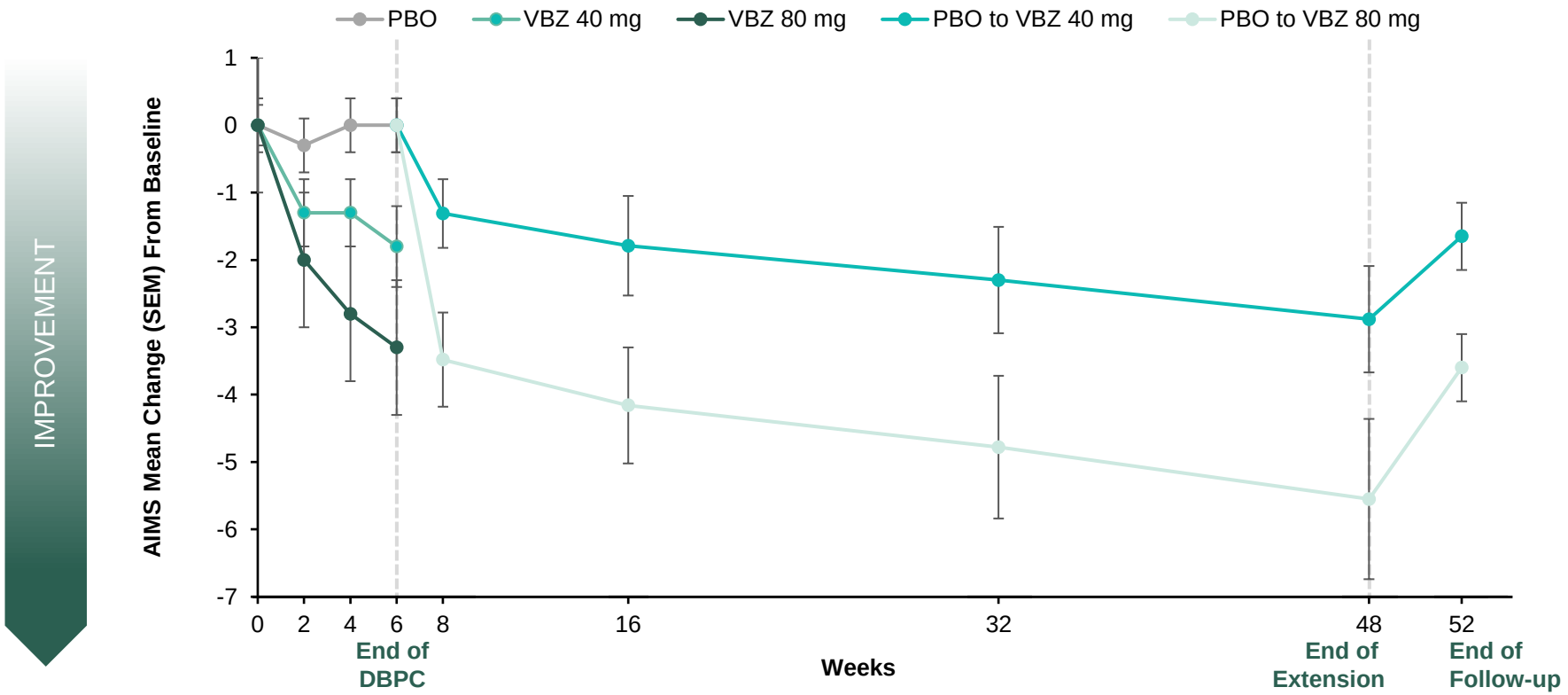


n value									
PBO	76	76	73	69					
VBZ 40 mg	70	70	64	63	59	50	37	34	34
VBZ 80 mg	79	77	73	70	67	58	50	43	41

AIMS, Abnormal Involuntary Movement Scale; DBPC, double-blind placebo-controlled; ITT, intent-to-treat; SEM, standard error of the mean; PBO, placebo; VBZ, valbenazine.
Data presented for ITT analysis set.

Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350.

KINECT 3 Extension: AIMS CFB for Rerandomized Groups

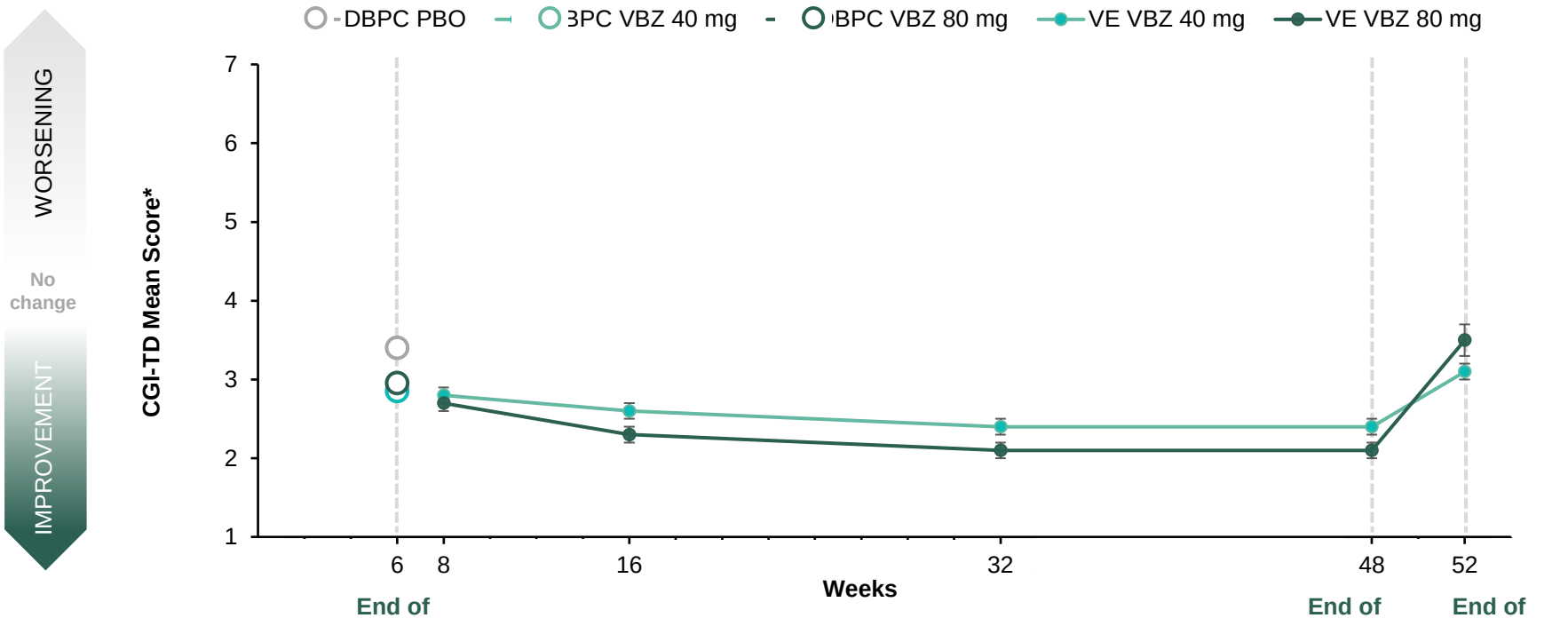


n value									
PBO	76	76	73	69					
VBZ 40 mg	70	70	64	63					
VBZ 80 mg	79	77	73	70					
PBO to VBZ 40 mg					32	29	27	24	24
PBO to VBZ 80 mg					33	31	27	22	22

AIMS, Abnormal Involuntary Movement Scale; DBPC, double-blind placebo-controlled; ITT, intent-to-treat; SEM, standard error of the mean; PBO, placebo; VBZ, valbenazine.
Data presented for ITT analysis set.

Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350.

KINECT 3 Extension: CGI-TD Scores

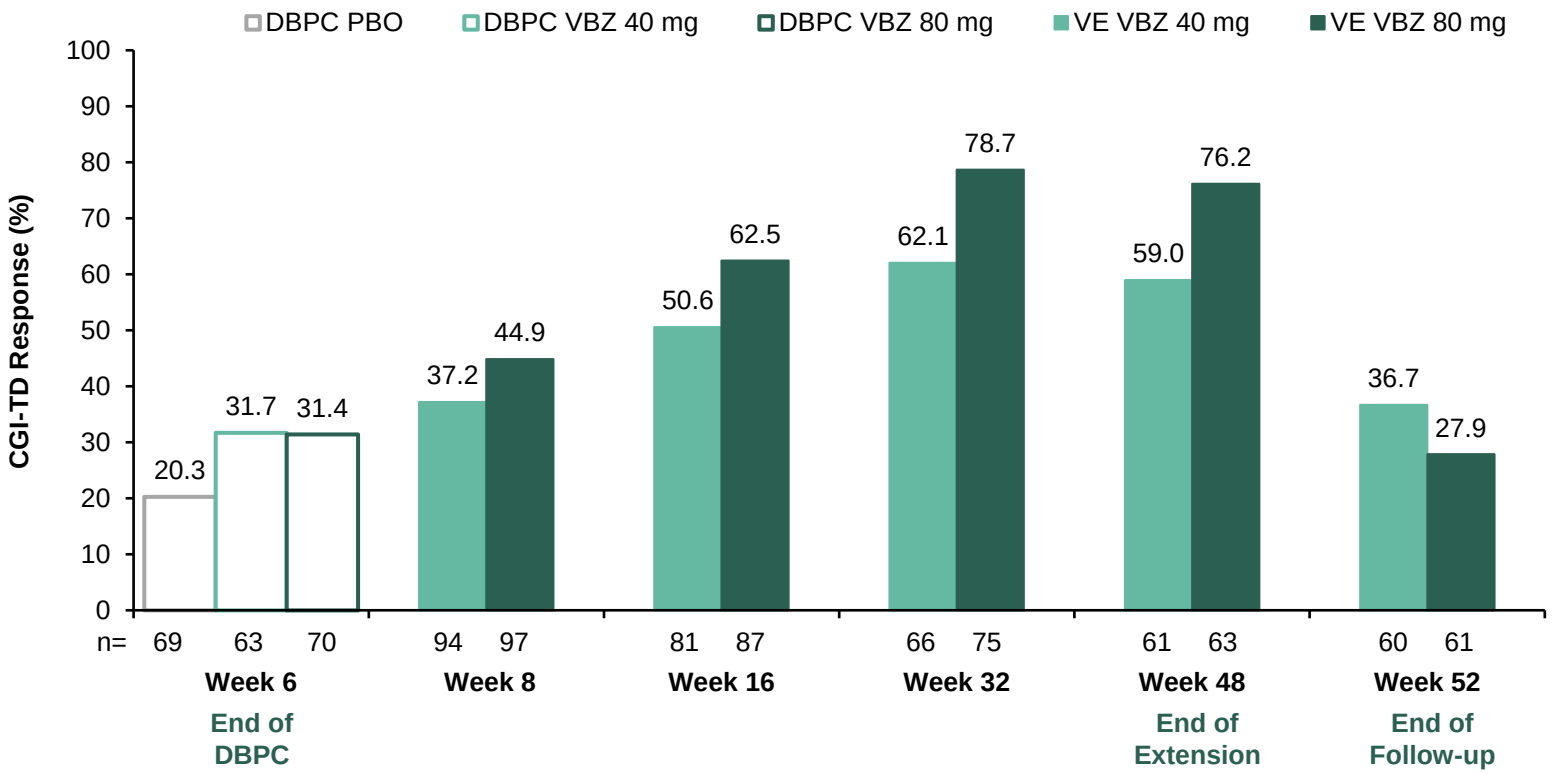


n value					
VBZ 40 mg	94	81	66	61	60
VBZ 80 mg	98	88	75	63	61

CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; DBPC, double-blind placebo-controlled; PBO, placebo; VBZ, valbenazine; VE, valbenazine extension.
At end of DBPC: no statistical difference between VBZ (80 or 40 mg) and PBO; based on least squares mean scores using a mixed-effects model for repeated measures.
VE and drug-free follow-up periods: results based on arithmetic mean scores with no imputation of missing values or significance testing between dose groups.
*Total change in condition rated as 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.

Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350.

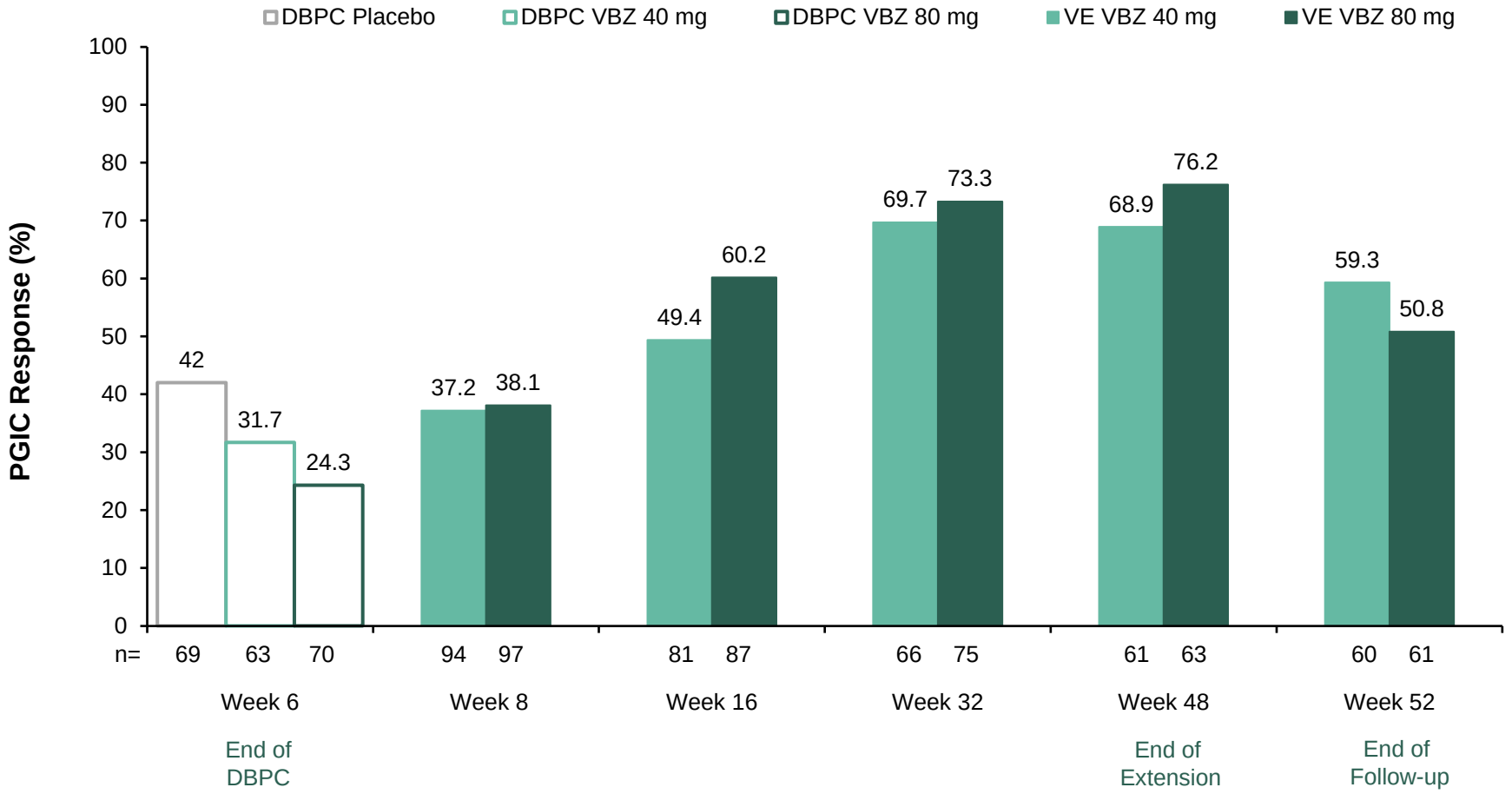
KINECT 3 Extension: CGI-TD Response*



CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; DBPC, double-blind placebo-controlled; VBZ, valbenazine; VE, valbenazine extension.
At end of DBPC: no statistical difference between VBZ (80 or 40 mg) and PBO, based on a 2-sided Cochran-Mantel-Haenszel analysis.
VE and drug-free follow-up periods: no significance testing between doses were performed.
*CGI-TD response: participants with CGI-TD rating of 1 (very much improved) or 2 (much improved).

Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350.

KINECT 3 Extension: PGIC Response*



*PGIC response: participants with CGI-TD rating of 1 (very much improved) or 2 (much improved).
At end of DBPC: no statistical difference between valbenazine (80 or 40 mg) and placebo, based on a 2-sided Cochran-Mantel-Haenszel analysis.
VE and drug-free follow-up periods: no significance testing between doses were performed.

DBPC, double-blind placebo-controlled; PGIC, Patient Global Impression of Change; VBZ, valbenazine; VE, valbenazine extension.

Factor SA, et al. *J Clin Psychiatry*. 2017;78(9):1344-1350.

AEs Leading to Discontinuation

6-week controlled and long-term extension period from KINECT 3

- In the placebo-controlled period, 5% of the placebo group, 6% of the valbenazine 40-mg group, and 6% of the valbenazine 80-mg group experienced AEs leading to discontinuation
  - **Placebo (all n=1):** Tourette syndrome, nausea, mental status change, schizoaffective disorder
  - **Valbenazine 40 mg (all n=1):** body tinea, akathisia, anxiety, bipolar disorder, hostility, mental status change
  - **Valbenazine 80 mg (all n=1):** acute hepatitis, jaundice, schizoaffective disorder, suicidal ideation, suicide attempt
- In the extension treatment period, 13% of the valbenazine 40-mg group and 18% of the valbenazine 80-mg group experienced AEs leading to discontinuation
  - **Valbenazine 40 mg (all n=1 unless noted):** fatigue, increased A1C, decreased hemoglobin, syncope, TIA, tremor, mental status change, psychotic disorder, schizophrenia, trance, hematuria, acute renal failure, rash, hospitalization for social circumstances, suicidal ideation (n=2)
  - **Valbenazine 80 mg (all n=1 unless noted):** constipation, hypersalivation, fatigue, gait disturbance, peripheral edema, hepatic failure, auto accident, decreased appetite, diabetes mellitus, hyperkalemia, metabolic acidosis, osteoarthritis, attention disturbance, TIA, tremor, suicidal behavior, suicidal ideation, suicide attempt, pleural effusion, DVT, asthenia (n=2), somnolence (n=3)

AE, adverse event; DVT, deep vein thrombosis; TIA, transient ischemic attack.
Data presented for safety analysis set.
Data on file. Neurocrine Biosciences, Inc.

Case 1: 54-year-old White Female With Mood Disorder (Bipolar 1)

Baseline AIMS score: 20

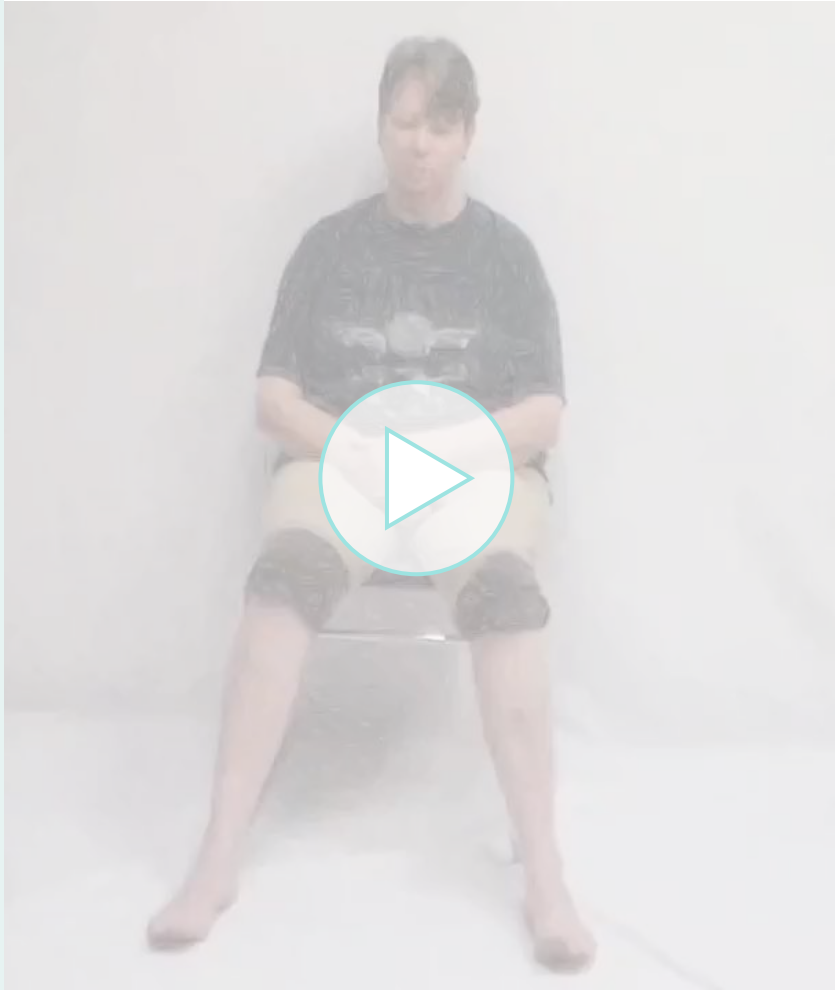
Age at TD diagnosis: 44

Comorbidities:

- Hypothyroid
- Generalized anxiety disorder
- Hypercholesterolemia

Relevant concomitant medications at baseline:

- Lithium
- Wellbutrin (bupropion)
- Artane (trihexyphenidyl)
- Klonopin (clonazepam)



Continue

AIMS, Abnormal Involuntary Movement Scale; TD, tardive dyskinesia.
Data on file. Neurocrine Biosciences, Inc.

Patients have consented to Neurocrine's use of this video and their protected health information.

Case 1: 54-year-old White Female With Mood Disorder (Bipolar 1)

Randomized to receive VBZ 80 mg:

- Week 6 AIMS score of 7

Continue

AIMS, Abnormal Involuntary Movement Scale; VBZ, valbenazine.

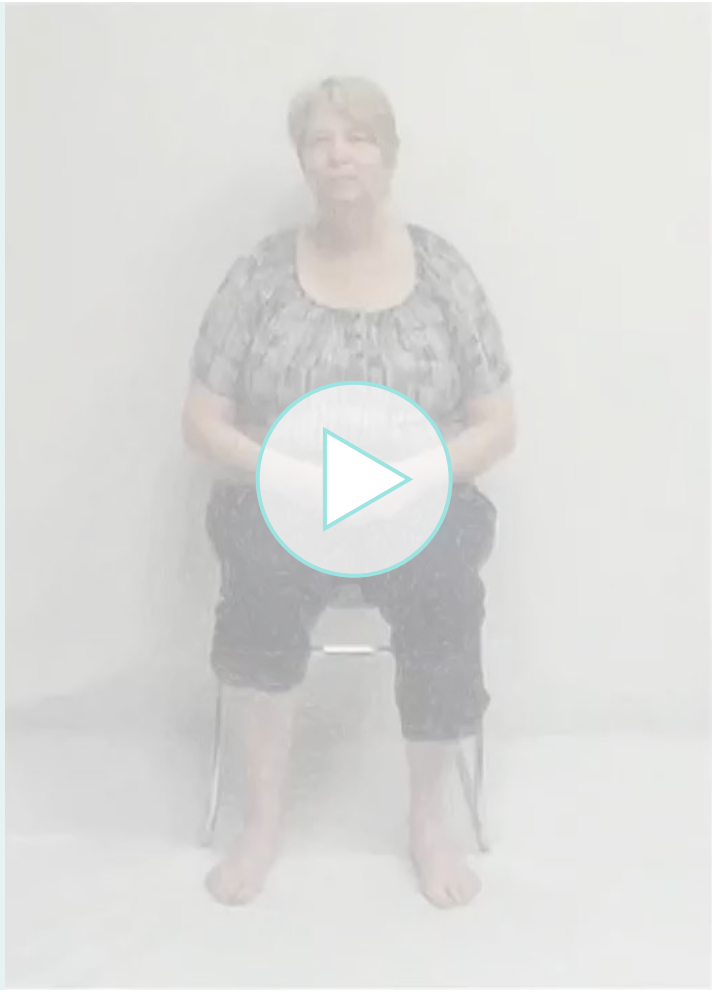
Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.
Data on file. Neurocrine Biosciences, Inc.

Patients have consented to Neurocrine's use of this video and their protected health information.

Case 1: 54-year-old White Female With Mood Disorder (Bipolar 1)

Remains on VBZ 80 mg:

- Week 48 AIMS score of 5



Continue

AIMS, Abnormal Involuntary Movement Scale; VBZ, valbenazine.

Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.
Data on file. Neurocrine Biosciences, Inc.

Patients have consented to Neurocrine's use of this video and their protected health information.

Case 1: 54-year-old White Female With Mood Disorder (Bipolar 1)

4 weeks after treatment discontinuation

- Week 52 AIMS score of 17

AIMS, Abnormal Involuntary Movement Scale.

Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.
Data on file. Neurocrine Biosciences, Inc.

Patients have consented to Neurocrine's use of this video and their protected health information.

Case 2: 44-year-old Hispanic Female With Mood Disorder (Major Depression)

Baseline AIMS score: 13

Age at TD diagnosis: unknown

Comorbidities:

- Anxiety
- Insomnia

Relevant concomitant medications at baseline:

- Zoloft (sertraline)
- Klonopin (clonazepam)
- Cogentin (benztropine)
- Seroquel (quetiapine)

Continue

AIMS, Abnormal Involuntary Movement Scale; TD, tardive dyskinesia.
Data on file. Neurocrine Biosciences, Inc.

Patients have consented to Neurocrine's use of this video and their protected health information.

Case 2: 44-year-old Hispanic Female With Mood Disorder (Major Depression)

Randomized to PBO:

- Week 6 AIMS score of 12

Continue

AIMS, Abnormal Involuntary Movement Scale; PBO, placebo.

Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-484.
Data on file. Neurocrine Biosciences, Inc.

Patients have consented to Neurocrine's use of this video and their protected health information.

Case 2: 44-year-old Hispanic Female With Mood Disorder (Major Depression)

Rerandomized to receive VBZ 80 mg:

- Week 48 AIMS score of 5

Continue

AIMS, Abnormal Involuntary Movement Scale; VBZ, valbenazine.

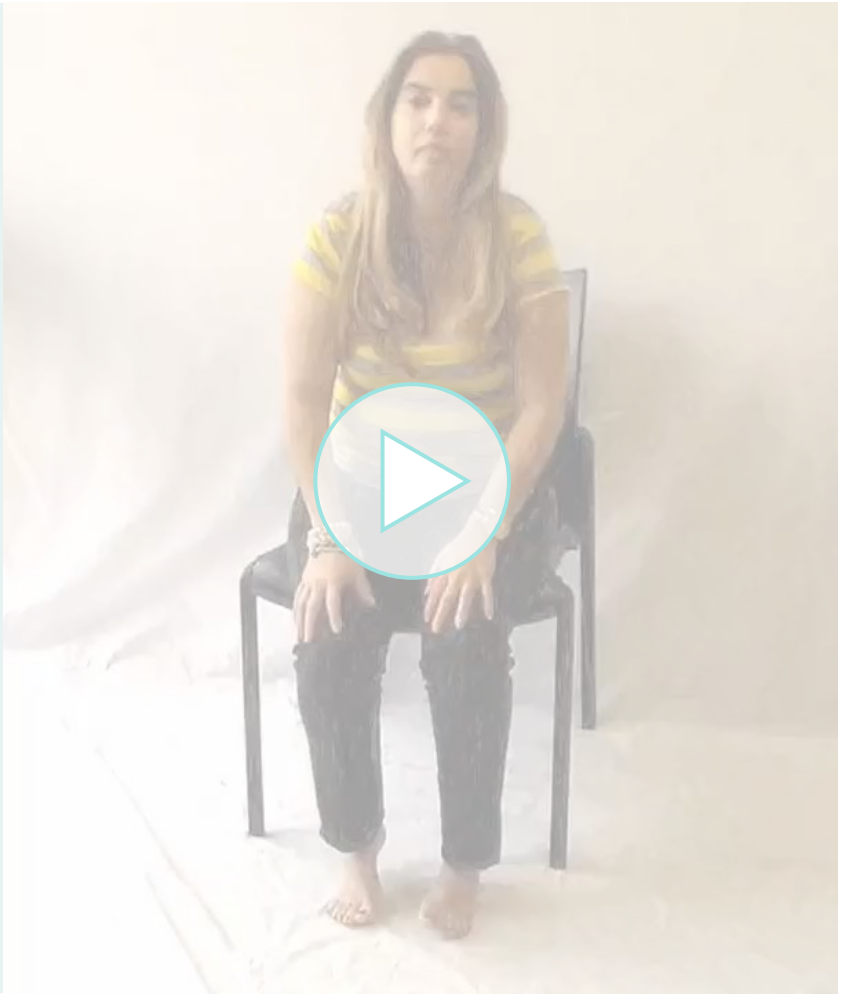
Hauser RA, et al. *Am J Psychiatry*. 2017;174(5):476-484.
Data on file. Neurocrine Biosciences, Inc.

Patients have consented to Neurocrine's use of this video and their protected health information.

Case 2: 44-year-old Hispanic Female With Mood Disorder (Major Depression)

4 weeks after treatment discontinuation

- Week 52 AIMS score of 14

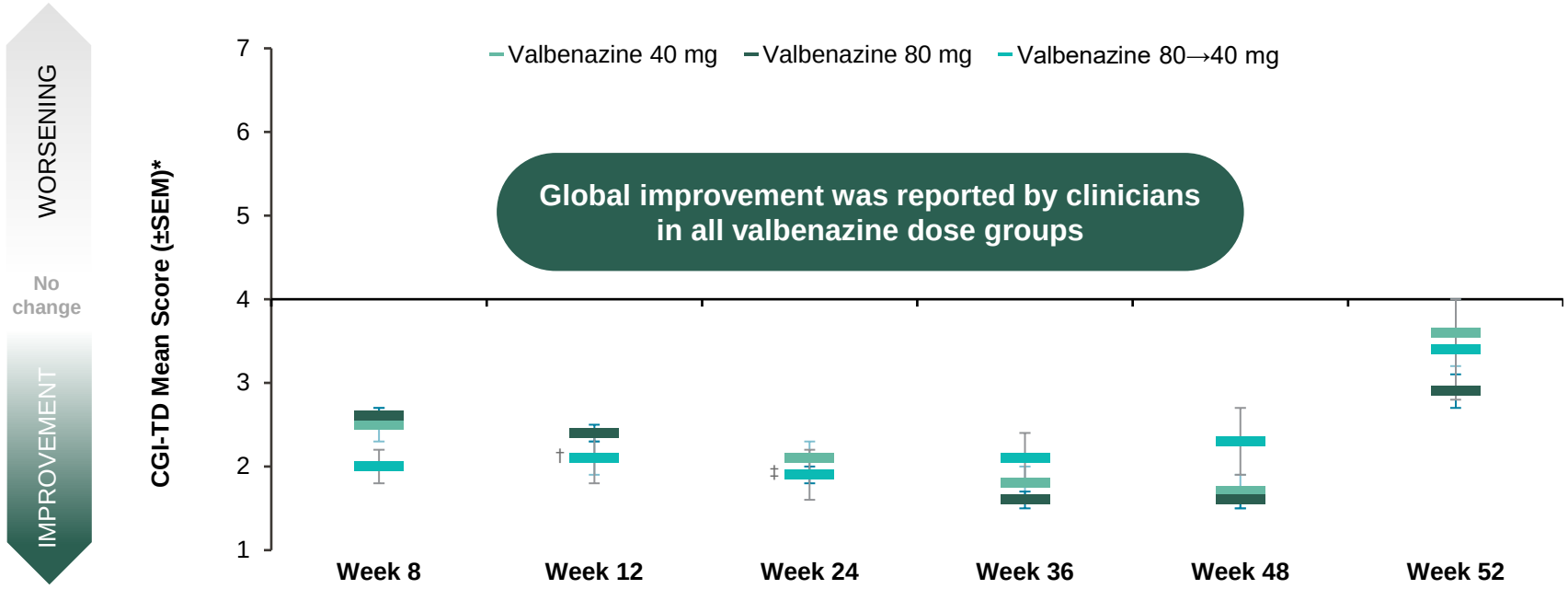


AIMS, Abnormal Involuntary Movement Scale.

Hauser RA, et al. *Am J Psychiatry*. 2017;174(5):476-484.
Data on file. Neurocrine Biosciences, Inc.

Patients have consented to Neurocrine's use of this video and their protected health information.

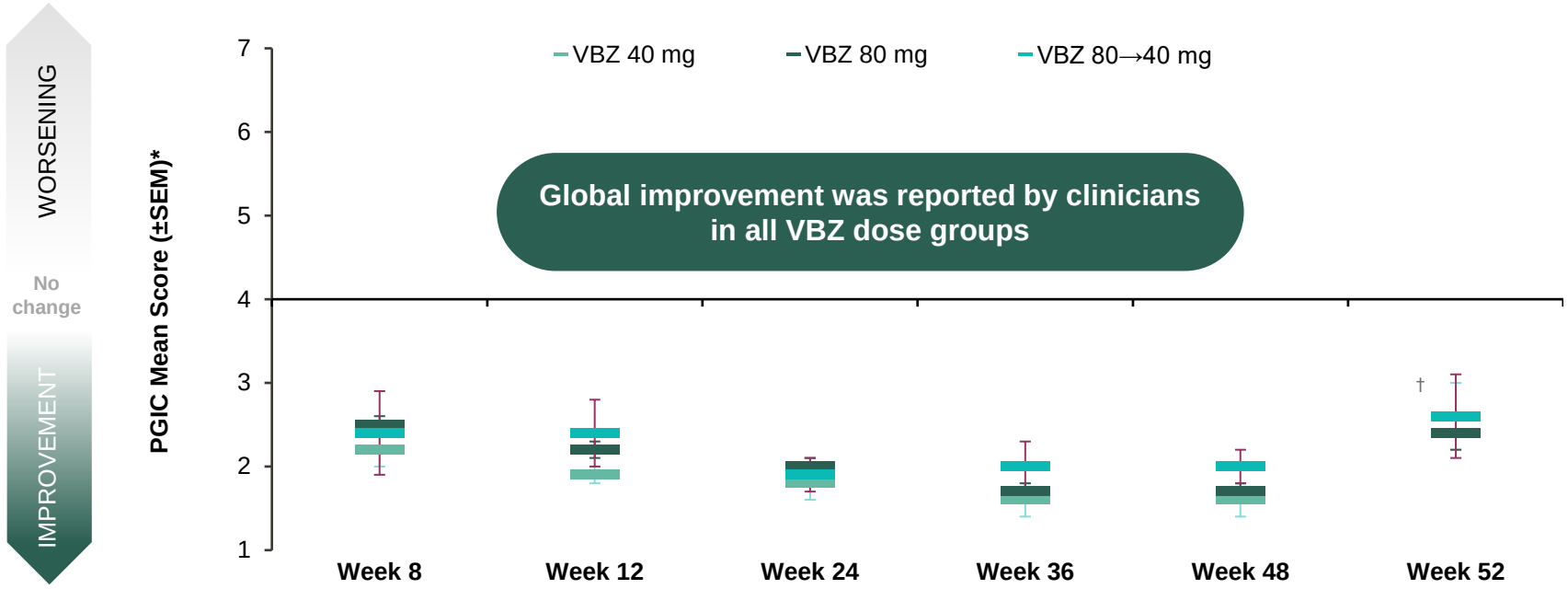
KINECT 4: CGI-TD Mean Score by Visit



	Week 8	Week 12	Week 24	Week 36	Week 48	Week 52
40 mg, n	33	30	25	20	20	20
80 mg, n	105	97	87	79	74	74
80→40 mg, n	11	11	10	9	9	9

CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; SEM, standard error of the mean.
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; 80→40 mg: dose reduction from 80 to 40 mg.
*Total change in condition rated as 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.
†Scores of the 40- and 80-mg→40-mg groups were equal.
‡Scores of the 80- and 80-mg→40-mg groups were equal.
Marder SR, et al. *ACNP 2017*; Palm Springs, CA.

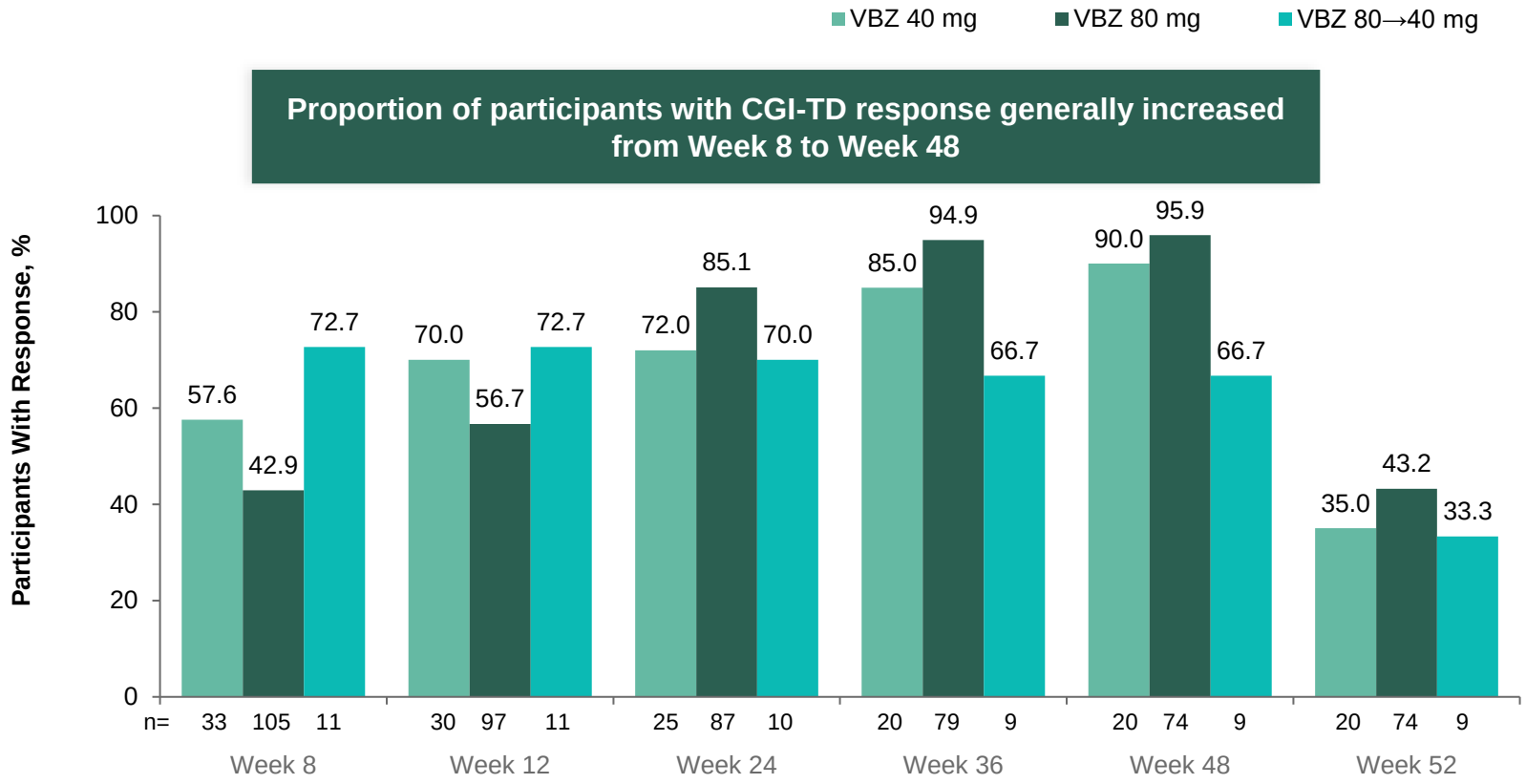
KINECT 4: PGIC Mean Score by Visit



	Week 8	Week 12	Week 24	Week 36	Week 48	Week 52
40 mg, n	33	30	25	19	20	20
80 mg, n	105	97	87	79	74	74
80→40 mg, n	11	11	10	9	9	9

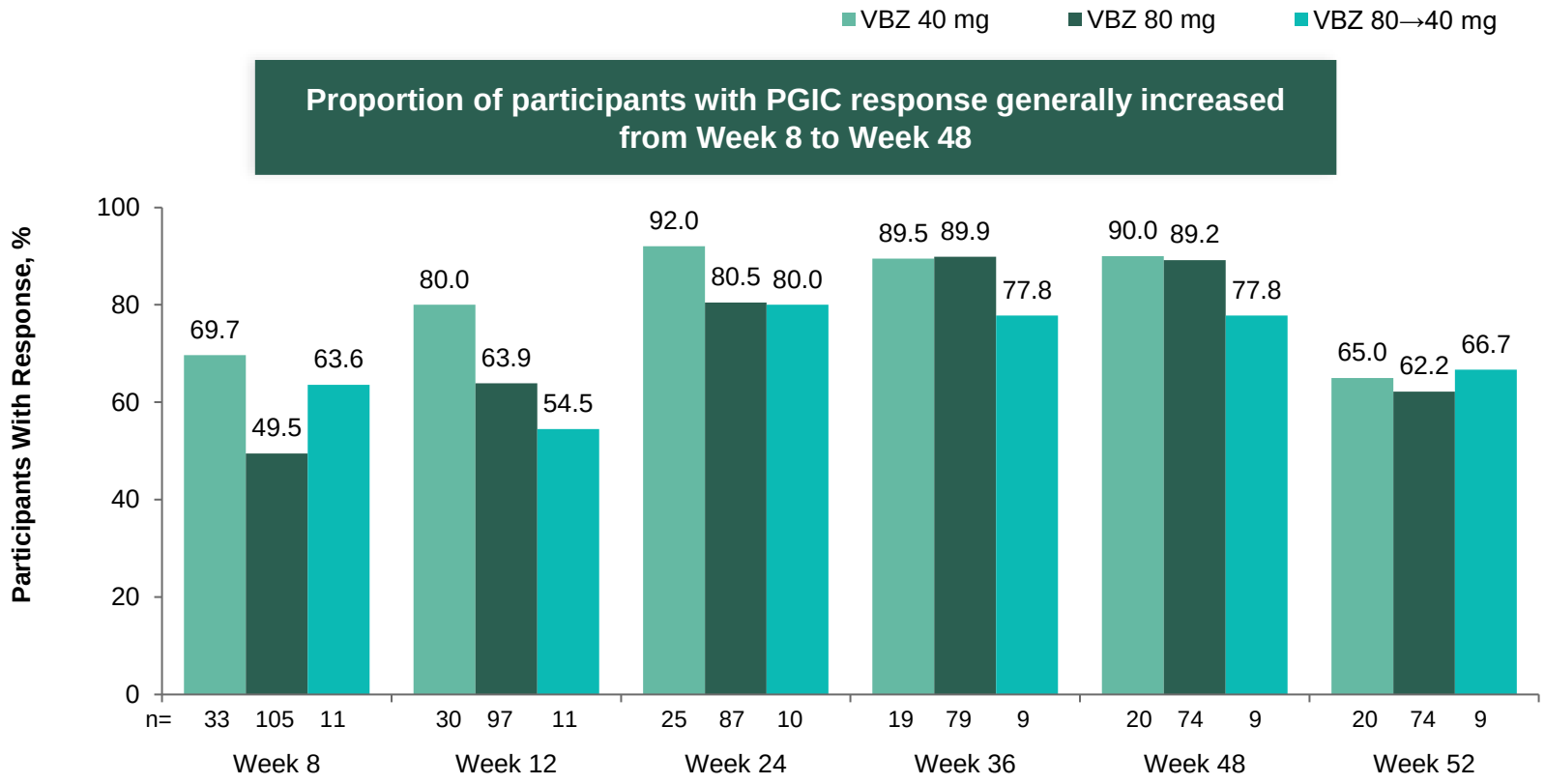
PGIC, Patient Global Impression of Change; SEM, standard error of the mean; VBZ, valbenazine.
40 mg: never had a dose increase to 80 mg; 80 mg: received 40 mg and increased to 80 mg, without a subsequent dose reduction; 80→40 mg: dose reduction from 80 to 40 mg.
*Total change in condition rated as 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse. †Scores of the 40- and 80-mg→40-mg groups were equal.
Marder SR, et al. ACNP 2017; Palm Springs, CA.

KINECT 4: CGI-TD Response* Rate by Visit

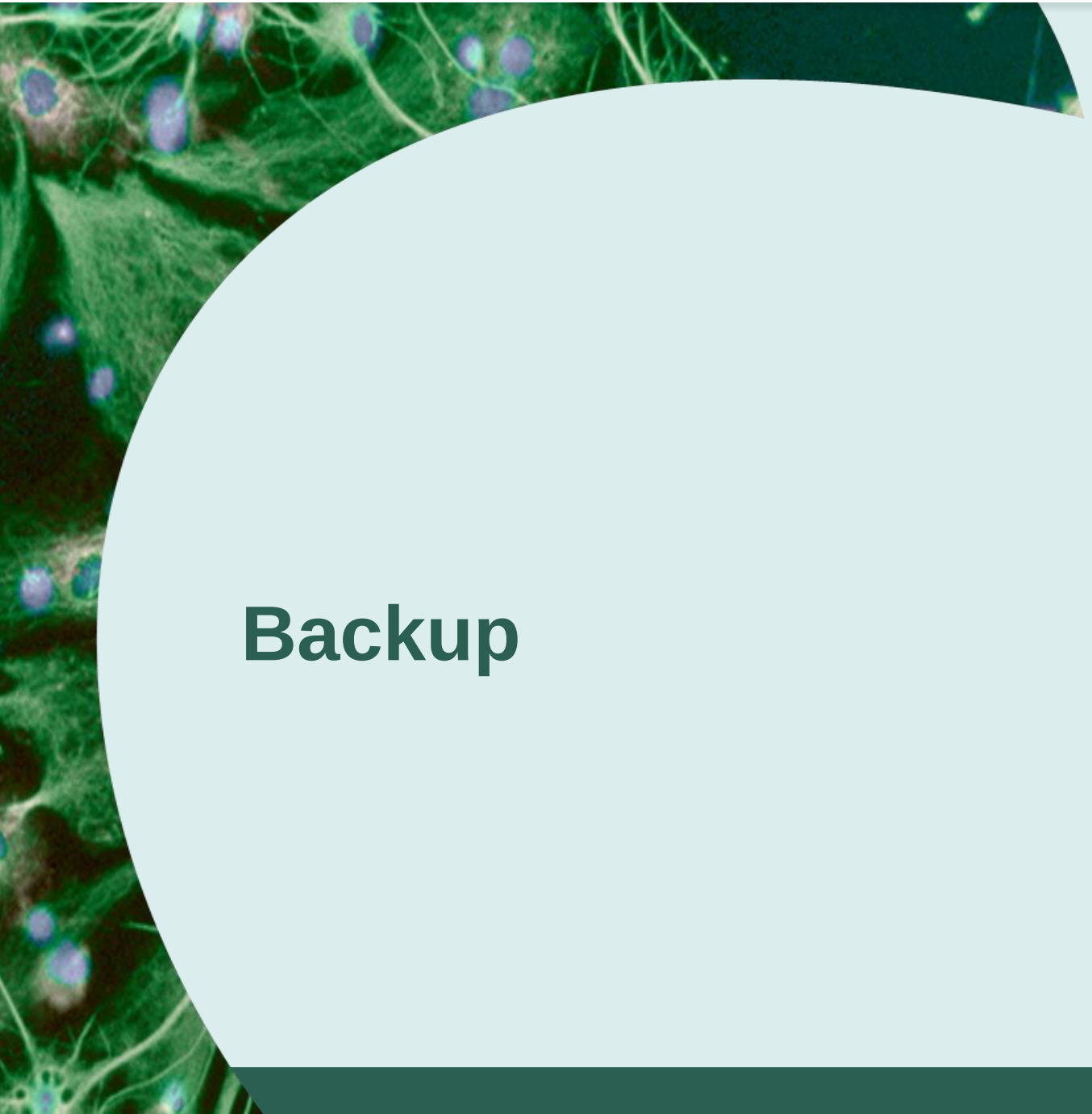


CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; VBZ, valbenazine.
40 mg: never had a dose increase to 80 mg; 80 mg: received 40 mg and increased to 80 mg, without a subsequent dose reduction; 80→40 mg: dose reduction from 80 to 40 mg.
*CGI-TD Score ≤2 (“Much Improved” or “Very Much Improved”).
Marder SR, et al. ACNP Congress 2017; Palm Springs, CA.

KINECT 4: PGIC Response* Rate by Visit



PGIC, Patient Global Impression of Change; VBZ, valbenazine.
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; 80→40 mg: dose reduction from 80 to 40 mg.
*PGIC score ≤2 (“Much Improved” or “Very Much Improved”).
Marder SR, et al. ACNP Congress 2017; Palm Springs, CA.



Backup

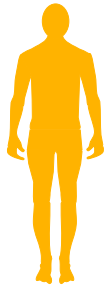
Backup Table of Contents

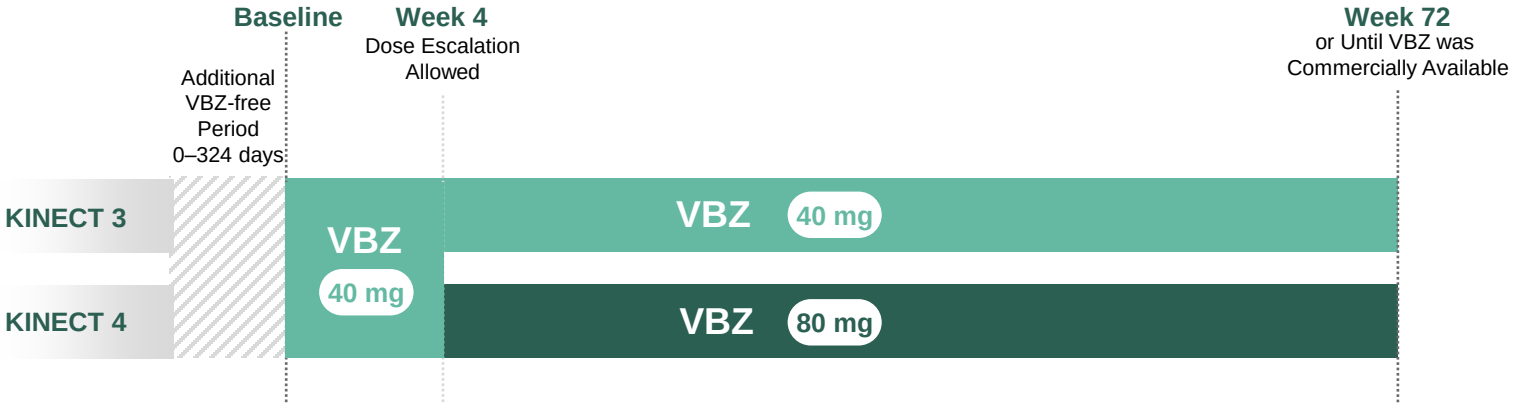
Study 1506 (NCT02736955): Long-term, Open-label Rollover Phase 3b Study

Study 1506: Study Design

Open-label rollover study

Participants who completed KINECT 3 or KINECT 4 N=161





Stable doses of concomitant medications to treat psychiatric disorders and comorbid medical conditions were allowed

Dosing

- All rollover study participants received once-daily 40 mg VBZ for 4 weeks
- At the end of Week 4, dose could be escalated to 80 mg 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

TD, tardive dyskinesia; VBZ, valbenazine.
Patients who received VBZ 80 mg in the 1506 study followed a different dosing schedule than those in the KINECT 3 pivotal study. In KINECT 3, patients had a dose increase from 40 to 80 mg after Week 1. In KINECT 4 and 1506, patients had a dose increase from 40 to 80 mg after Week 4. The impact of this on long-term effectiveness is not known.
Lindenmayer JP, et al. *ASCP 2018*; Miami, FL.

Study 1506: Assessments

Efficacy

- All outcomes were analyzed descriptively in participants who received ≥1 dose of study drug and had ≥1 available postbaseline assessment
- Mean CGIS-TD scores were analyzed at every 12-week visit
- Percentages of participants with a CGIS-TD score of 1 (“normal, not at all ill”) or 2 (“borderline ill”) were also analyzed

Safety

Safety assessments included

- TEAEs
- Laboratory tests
- Vital sign measurements
- ECGs
- C-SSRS

CGIS-TD, Clinical Global Impression of Severity-Tardive Dyskinesia; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; TEAE, treatment-emergent adverse event.
Lindenmayer JP, et al. ASCP 2018; Miami, FL.

Study 1506: Eligibility Criteria

Key inclusion criteria

- Adults with neuroleptic-induced TD and a DSM psychiatric diagnosis (ie, schizophrenia, schizoaffective disorder, or mood disorder) who completed KINECT 3 or KINECT 4
- Psychiatrically stable before study entry (Brief Psychiatric Rating Scale score <50 at screening)

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 (C-SSRS) or violent behavior

C-SSRS, Columbia-Suicide Severity Rating Scale; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; TD, tardive dyskinesia.
Lindenmayer JP, et al. ASCP 2018; Miami, FL.

Study 1506: Baseline Characteristics

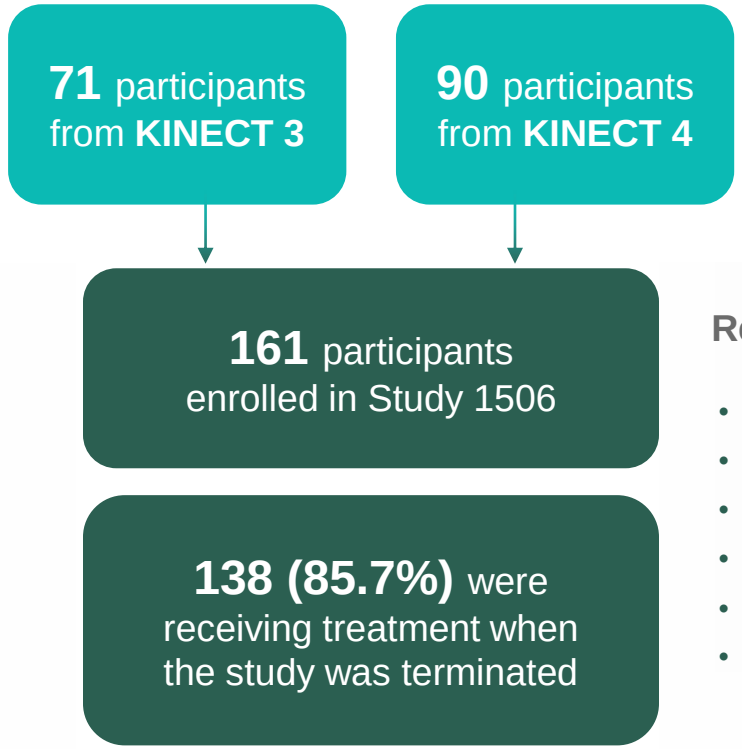
Baseline characteristics were generally similar across treatment groups

	VBZ 40 mg (n=35)	VBZ 80 mg (n=117)	All Participants (n=160)*
Age, mean (SD), years	57.3 (8.9)	57.9 (8.8)	57.9 (8.8)
Male, n (%)	13 (37.1)	63 (53.8)	81 (50.6)
Race, n (%)			
White	21 (60.0)	86 (73.5)	111 (69.4)
Black	14 (40.0)	30 (25.6)	47 (29.4)
BMI, mean (SD), kg/m^2	29.2 (5.5)	28.5 (5.5)	28.8 (5.5)
Primary psychiatric diagnosis, n (%)			
Schizophrenia/schizoaffective disorder	23 (65.7)	75 (64.1)	104 (65.0)
Mood disorder	12 (34.3)	42 (35.9)	56 (35.0)
Age at diagnosis, mean (SD), years			
Schizophrenia/schizoaffective disorder	27.1 (8.3)	28.7 (11.4)	28.2 (10.6)
Mood disorder	36.0 (12.0)	33.9 (13.3)	34.7 (13.2)
TD	48.3 (11.2)	48.4 (9.5)	48.0 (10.1)
BPRS total score, mean (SD)	27.3 (6.3)	26.1 (5.6)	26.6 (6.0)
CGIS-TD score, mean (SD)	3.9 (1.1)	3.9 (1.3)	3.9 (1.2)
C-SSRS lifetime at screening, n (%)			
Suicidal ideation	10 (28.6)	36 (30.8)	49 (30.6)
Suicidal behavior	10 (28.6)	32 (27.4)	44 (27.5)

The percentage of all participants taking ≥1 antipsychotic medication before the study (81.9%) was similar to the percentage during the study (82.5%)

*Includes 8 participants who had a dose reduction from 80 to 40 mg after Week 4.
BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CGIS-TD, Clinical Global Impression of Severity-Tardive Dyskinesia; C-SSRS, Columbia-Suicide Severity Rating Scale; SD, standard deviation; TD, tardive dyskinesia.
Lindenmayer JP, et al. ASCP 2018; Miami, FL.

Study 1506: Results



1 participant without postbaseline data was excluded from analyses

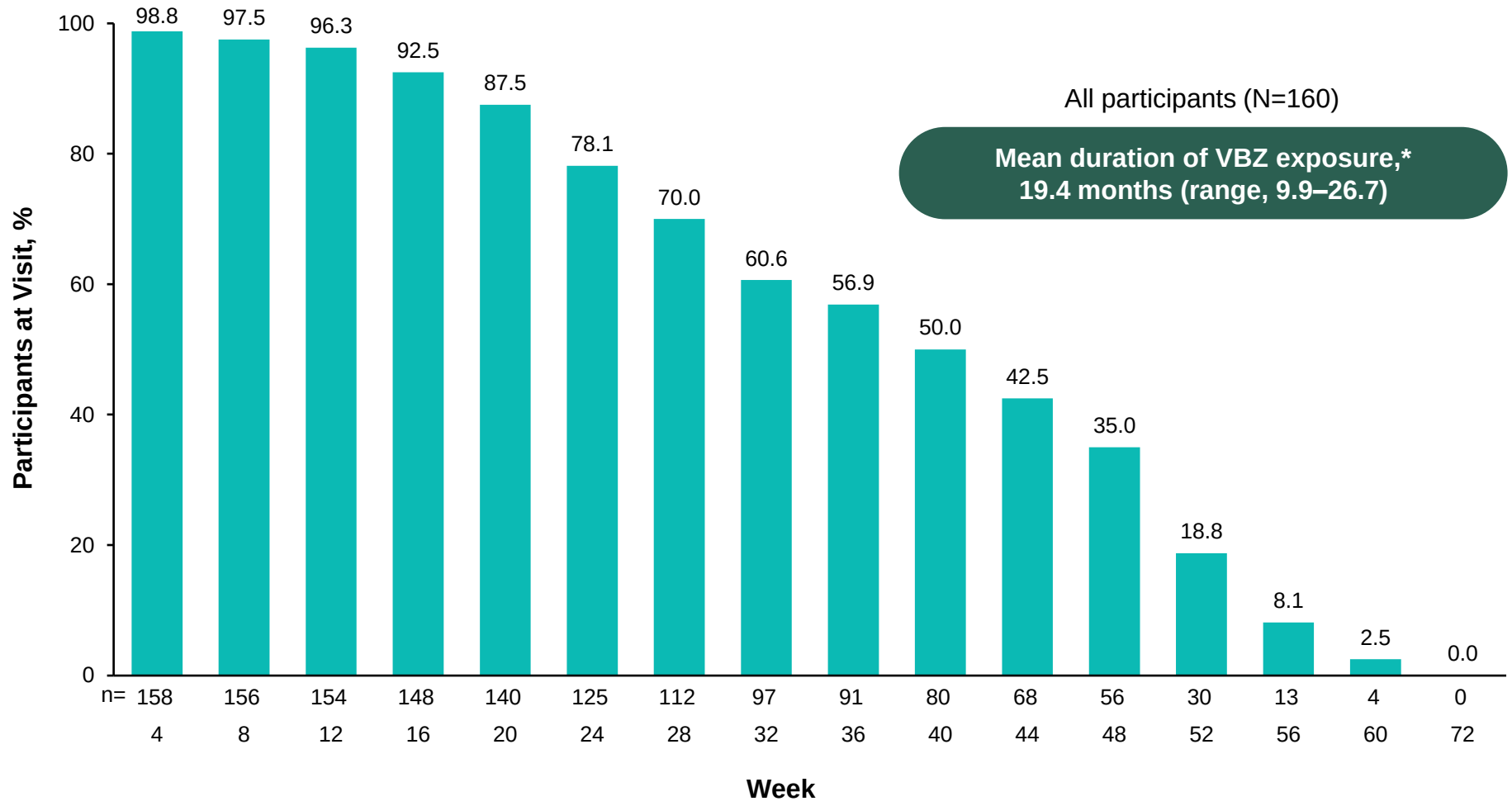
Reasons for discontinuation

- Withdrawal of consent (n=8)
- Adverse events (n=5)
- Death (n=4, not related to treatment)
- Noncompliance (n=3)
- Investigator decision (n=2)
- Lost to follow-up (n=1)

Few participants reached Week 60 (n=4) and none reached Week 72 (n=0) because valbenazine became commercially available before reaching those visits

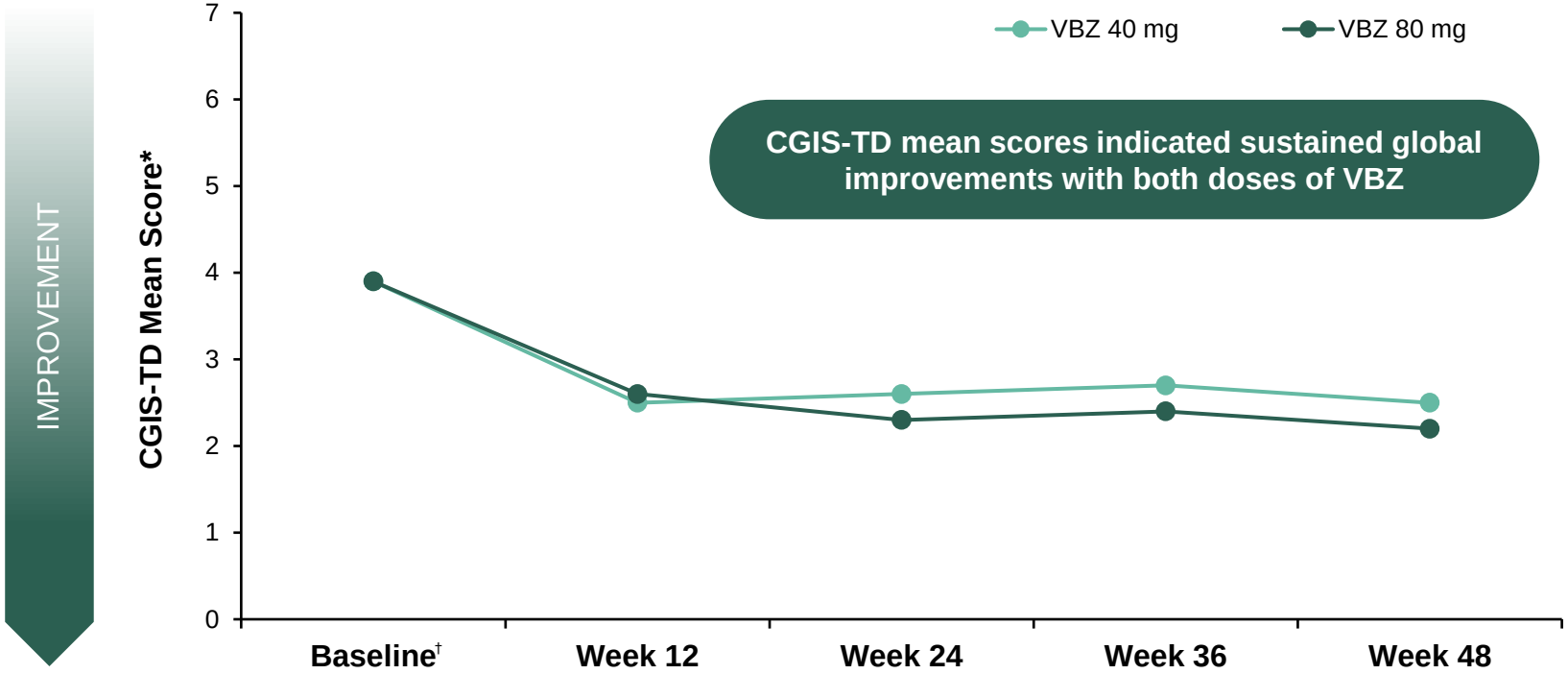
Lindenmayer JP, et al. ASCP 2018; Miami, FL.

Study 1506: Participants Completing Each Study Visit



VBZ, valbenazine.
*From KINECT 3 or KINECT 4 baseline through end of rollover treatment.
Lindenmayer JP, et al. ASCP 2018; Miami, FL.

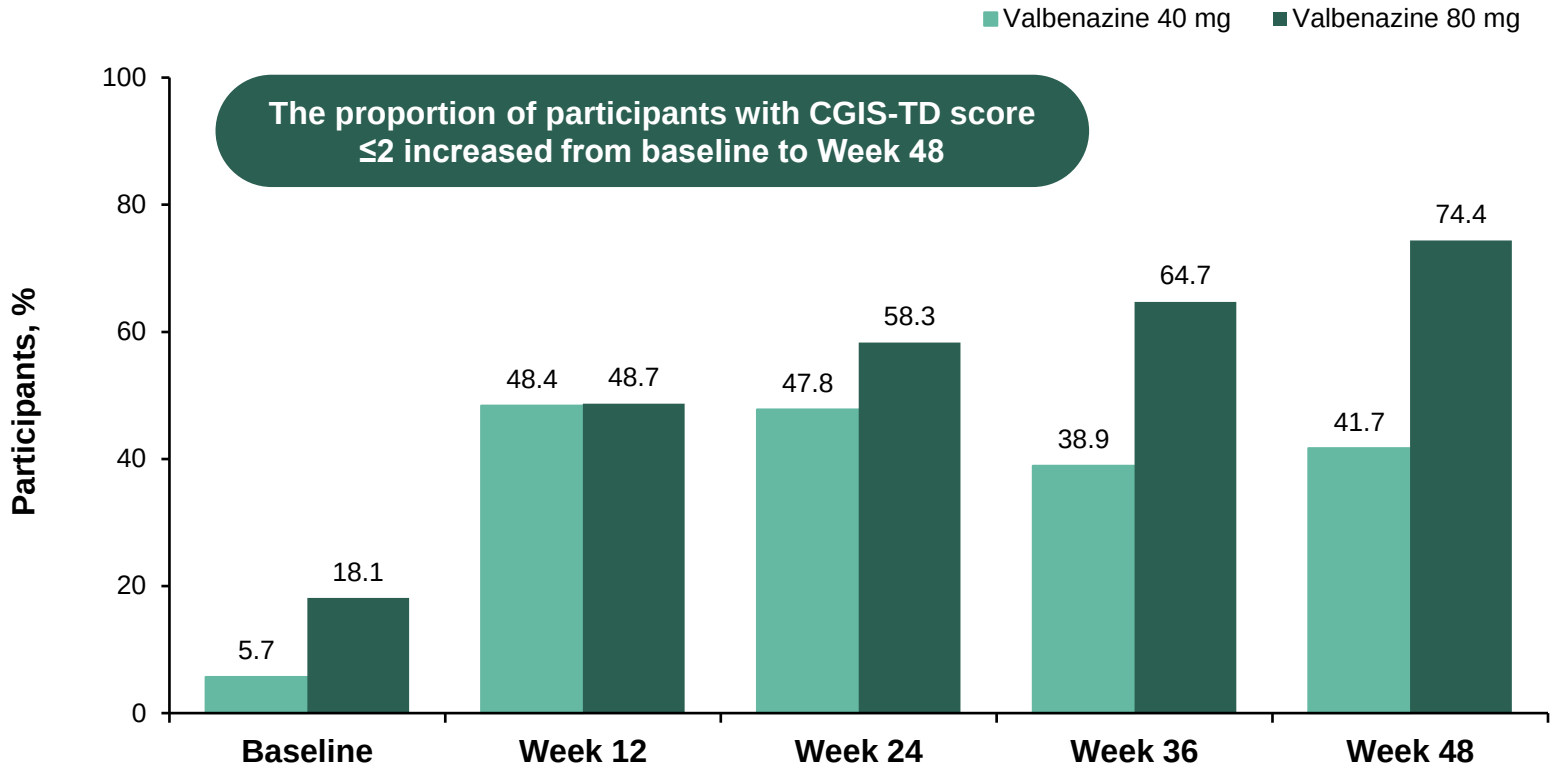
Study 1506: CGIS-TD Mean Score by Visit



	Baseline†	Week 12	Week 24	Week 36	Week 48
40 mg, n=	35	31	23	18	12
80 mg, n=	116	115	96	68	39

CGIS-TD, Clinical Global Impression of Severity-Tardive Dyskinesia; VBZ, valbenazine.
Data not shown for participants who had a dose reduction from 80 to 40 mg (n=8) or any participant who completed the Week 60 visit (total n=4) due to the small sample sizes of these groups.
.*Rated as 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill. †Baseline of rollover study.
Lindenmayer JP, et al. *ASCP 2018*; Miami, FL.

Study 1506: CGIS-TD Score ≤2 by Visit



40 mg, n/N	2/35	15/31	11/23	7/18	5/12
80 mg, n/N	21/116	56/115	56/96	44/68	29/39

CGIS-TD, Clinical Global Impression of Severity-Tardive Dyskinesia.
Data not shown for participants who had a dose reduction from 80 to 40 mg (n=8) or any participant who completed the Week 60 visit (total n=4) due to the small sample sizes of these groups.
*Baseline of rollover study.
Lindenmayer JP, et al. ASCP 2018; Miami, FL.

Study 1506: Safety and Tolerability

TEAEs

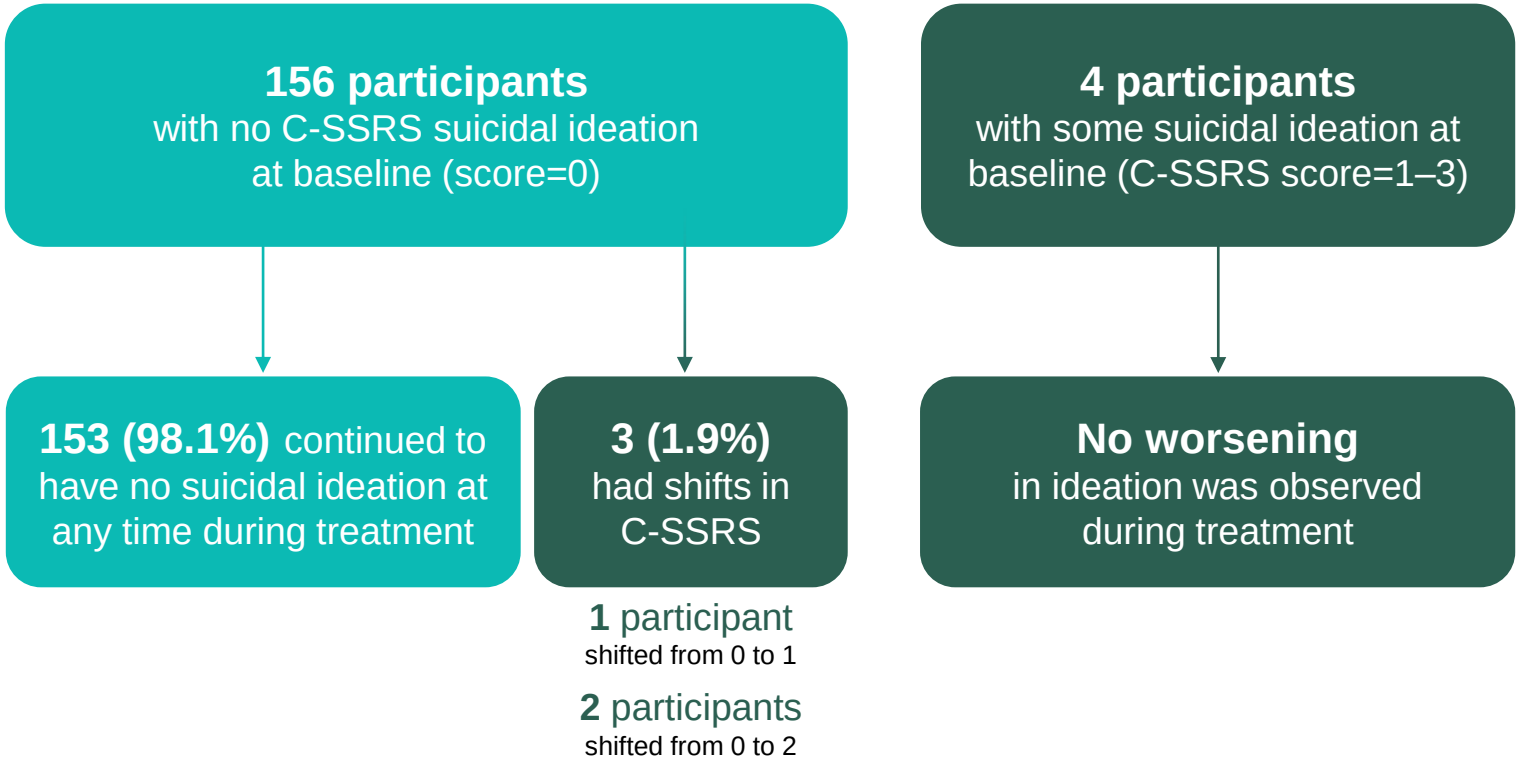
	Baseline to Week 4	Week 4 to End of Study		
	VBZ 40 mg (n=160)	VBZ 40 mg (n=32)	VBZ 80 mg (n=117)	All Participants (n=157)*
Summary, n (%)				
Any TEAE	15 (9.4)	14 (43.8)	56 (47.9)	77 (49.0)
Any serious TEAE	2 (1.3)	2 (6.3)	10 (8.5)	14 (8.9)
Any TEAE leading to discontinuation	2 (1.3)	0	6 (5.1)	7 (4.5)
Death	0	0	3 (2.6)	4 (2.5)†
TEAE by preferred term, n (%)‡				
Back pain	1 (0.6)	2 (6.3)	5 (4.3)	7 (4.5)
Urinary tract infection	0	1 (3.1)	6 (5.1)	7 (4.5)
Upper respiratory tract infection	0	1 (3.1)	5 (4.3)	6 (3.8)
Cough	1 (0.6)	1 (3.1)	3 (2.6)	5 (3.2)
Headache	0	1 (3.1)	4 (3.4)	5 (3.2)
Tremor	0	0	3 (2.6)	5 (3.2)
Fall	1 (0.6)	1 (3.1)	3 (2.6)	4 (2.5)
Nasopharyngitis	0	1 (3.1)	3 (2.6)	4 (2.5)
Somnolence	2 (1.3)	0	0	4 (2.5)
Suicidal ideation	0	1 (3.1)	3 (2.6)	4 (2.5)

TEAE, treatment-emergent adverse event; VBZ, valbenazine.
*Includes 8 participants who had a dose reduction from 80 to 40 mg after Week 4. †Deaths occurred due to chronic obstructive pulmonary disease, sepsis syndrome, alcohol-induced coma, and hypertensive heart disease; none were judged as treatment-related. ‡Reported in ≥2% of all participants from Week 4 to end of study.

Lindenmayer JP, et al. ASCP 2018; Miami, FL.

Study 1506: Safety and Tolerability

Suicidal ideation and other safety evaluations



Change from baseline in vital signs, ECG parameters, and laboratory test values were generally small and not clinically meaningful

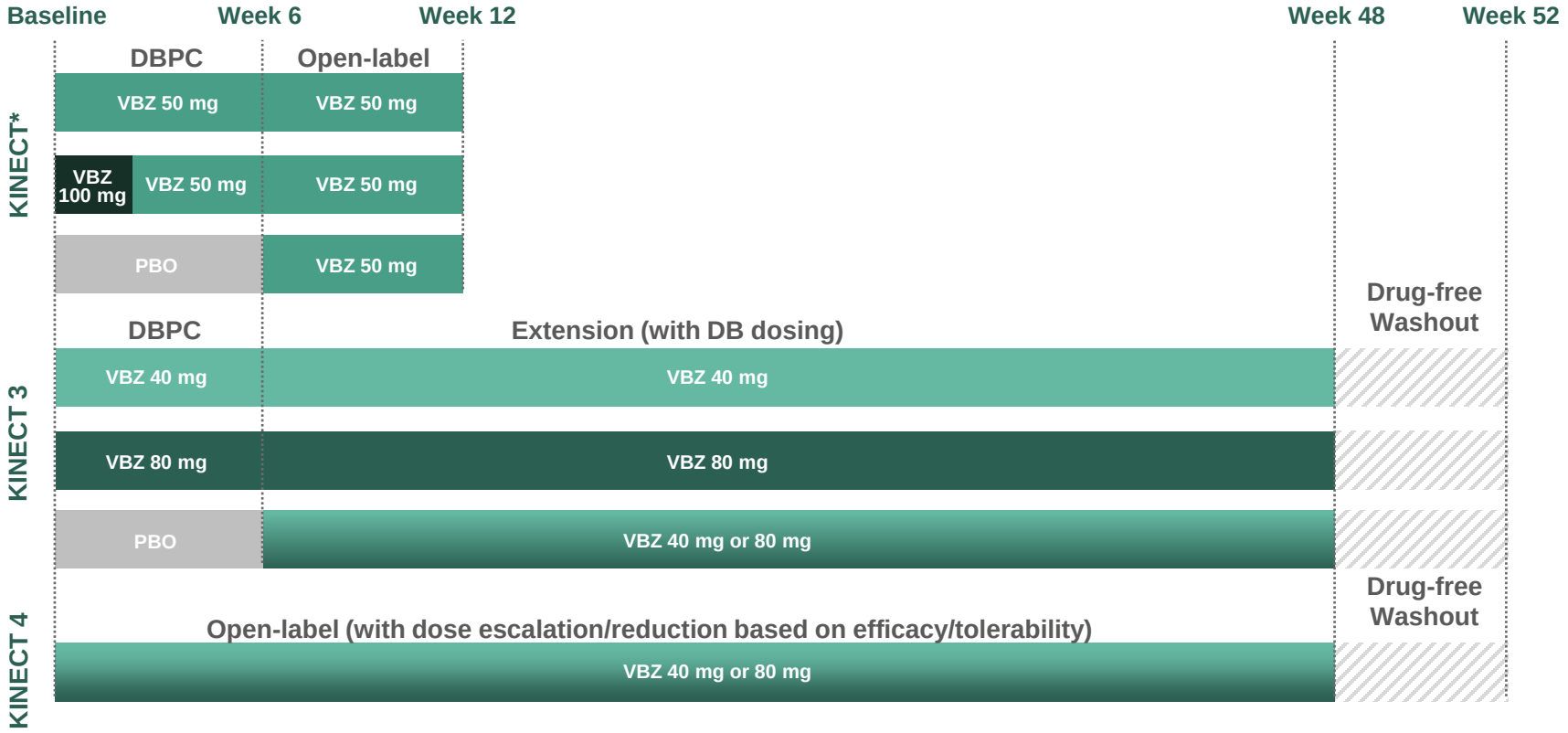
C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram.

Lindenmayer JP, et al. ASCP 2018; Miami, FL.

KINECT, KINECT 3, & KINECT 4: Pooled Long-term Safety Analysis

Pooled LTE From 3 Studies

VBZ-treated participants from KINECT, KINECT 3, and KINECT 4



Pooled LTE 40-mg group (3 studies):

- KINECT (50-mg group including those who initially received VBZ 100 mg for 2 weeks)
- KINECT 3 (40-mg group)
- KINECT 4 (40-mg group)

Pooled LTE 80-mg group (2 studies):

- KINECT 3 (80 mg)
- KINECT 4 (80 mg)

DBPC, double-blind placebo-controlled; LTE, long-term exposure; PBO, placebo VBZ, valbenazine.
KINECT and KINECT 3 are completed. KINECT 4 is completed. Final data analysis is pending.
*KINECT, 100 mg for 2 weeks.

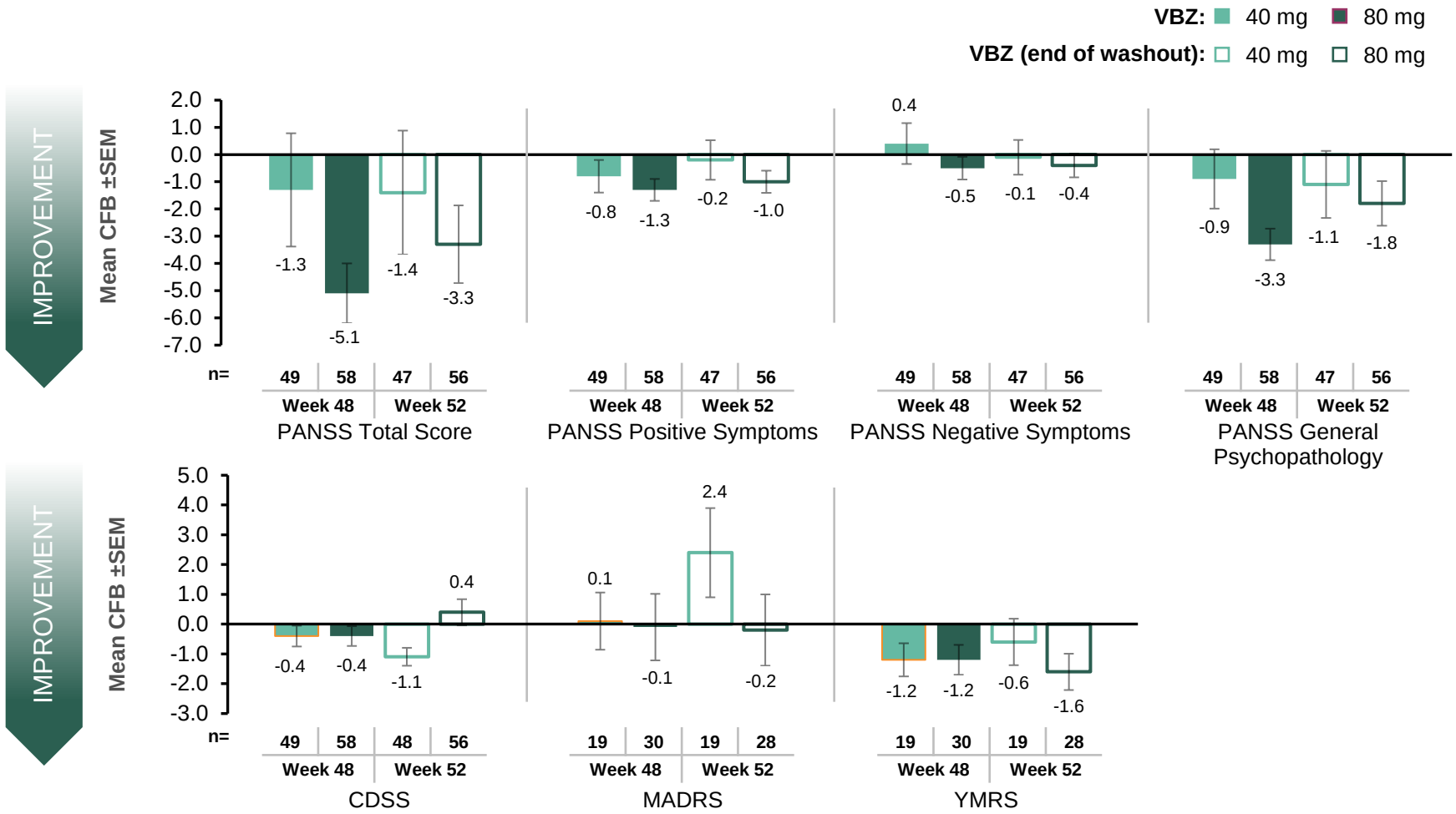
Remington G, et al. ACNP 2016. Hollywood, FL.

KINECT, KINECT 3, & KINECT 4 Pooled Long-Term Safety Analysis: Baseline Characteristics (Safety Population)*

	VBZ 40 mg (n=197)	VBZ 80 mg (n=230)	All Participants (n=427)
Age, mean years	56.2	56.9	56.6
<65 years, %	81.7	81.3	81.5
Male, %	59.4	52.2	55.5
White, %	56.3	65.7	61.4
Black, %	37.6	31.3	34.2
BMI			
Mean, kg/m^2	28.1	28.4	28.2
25 to <30, %	33.5	35.7	34.7
≥30, %	36.5	35.7	36.1
Mean age at TD diagnosis, years	48.6	48.2	48.4
Psychiatric diagnosis and history, %			
Current schizophrenia/schizoaffective disorder	76.6	67.4	71.7
Current mood disorder	23.4	32.6	28.3
Lifetime history of suicidality†	39.1	40.4	39.8
Concomitant use of antipsychotics, %			
Any concomitant antipsychotic	88.3	83.0	85.5
Atypical only	71.6	68.3	69.8
Typical only or both	16.8	14.8	15.7
Psychiatric scales, mean			
PANSS total‡	57.2	49.8	53.5
PANSS positive symptoms‡	13.4	11.5	12.4
PANSS negative symptoms‡	15.4	13.5	14.5
PANSS general psychopathology‡	28.4	24.8	26.6
CDSS total‡	2.4	1.9	2.1
MADRS total§	6.2	5.5	5.7
YMRS total§	2.6	2.5	2.5

BMI, body mass index; CDSS, Calgary Depression Scale for Schizophrenia; C-SSRS, Columbia-Suicide Severity Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; TD, tardive dyskinesia; VBZ, valbenazine; YMRS, Young Mania Rating Scale.
*As of 12/5/2016, baseline data not available for 3 participants. †Lifetime history of suicidality was defined as endorsement of any C-SSRS category for suicidal ideation (category 1–5) or suicidal behavior (category 6–10). ‡PANSS and CDSS were administered only to participants with schizophrenia/schizoaffective disorder (40 mg, n=154; 80 mg, n=155). §YMRS and MADRS were administered only to participants with mood disorder (40 mg, n=46; 80 mg, n=75).
Remington G, et al. ACNP 2016; Hollywood, FL.

KINECT, KINECT 3, & KINECT 4 Pooled Long-term Safety Analysis: Mean Changes in Psychiatric Scales Scores



CDSS, Calgary Depression Scale for Schizophrenia; CFB, change from baseline; 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.

PANSS and CDSS were administered only to participants with schizophrenia/schizoaffective disorder (40 mg, n=154; 80 mg, n=155). YMRS and MADRS were administered only to participants with mood disorder (40 mg, n=46; 80 mg, n=75).

Remington G, et al. ACNP 2016; Hollywood, FL.

KINECT, KINECT 3, & KINECT 4 Pooled Long-term Safety Analysis: AEs

	VBZ Dose Groups		All Participants (n=430)
	40 mg (n=200)	80 mg (n=230)	
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
AEs 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
Suicidal ideation‡	4.5	4.8	4.7
Dizziness	3.0	5.2	4.2
Diarrhea	3.0	4.8	4.0
Nasopharyngitis	3.0	4.3	3.7
Constipation	3.5	3.9	3.7
Depression	5.0	2.2	3.5
Vomiting	3.5	3.5	3.5
Anxiety	3.5	3.5	3.5
Fall	3.5	3.0	3.3
Dry mouth	4.0	2.2	3.0

- Laboratory parameters were similar across treatment groups; no clinically relevant changes were identified, including liver function tests and metabolic parameters
- Some participants had a small increase in prolactin levels; approximately 20% of all participants already had elevated prolactin at baseline
- No notable ECG changes were observed

*Serious AEs that occurred in ≥1% of all participants were schizophrenia (1.2%) and suicidal ideation (1.2%). †Reported in ≥3% of all VBZ-treated participants. ‡Includes spontaneous patient-reported TEAEs and endorsements of any C-SSRS suicidal ideation category (items 1–5).

AE, adverse event; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; TEAE, treatment-emergent adverse event; VBZ, valbenazine.

Remington G, et al. ACNP 2016; Hollywood, FL.