Time Course of Valbenazine Treatment in Tardive Dyskinesia

Early Improvement, Durability of Response, and Impact of Treatment Withdrawal

NEUROCRINE® BIOSCIENCES

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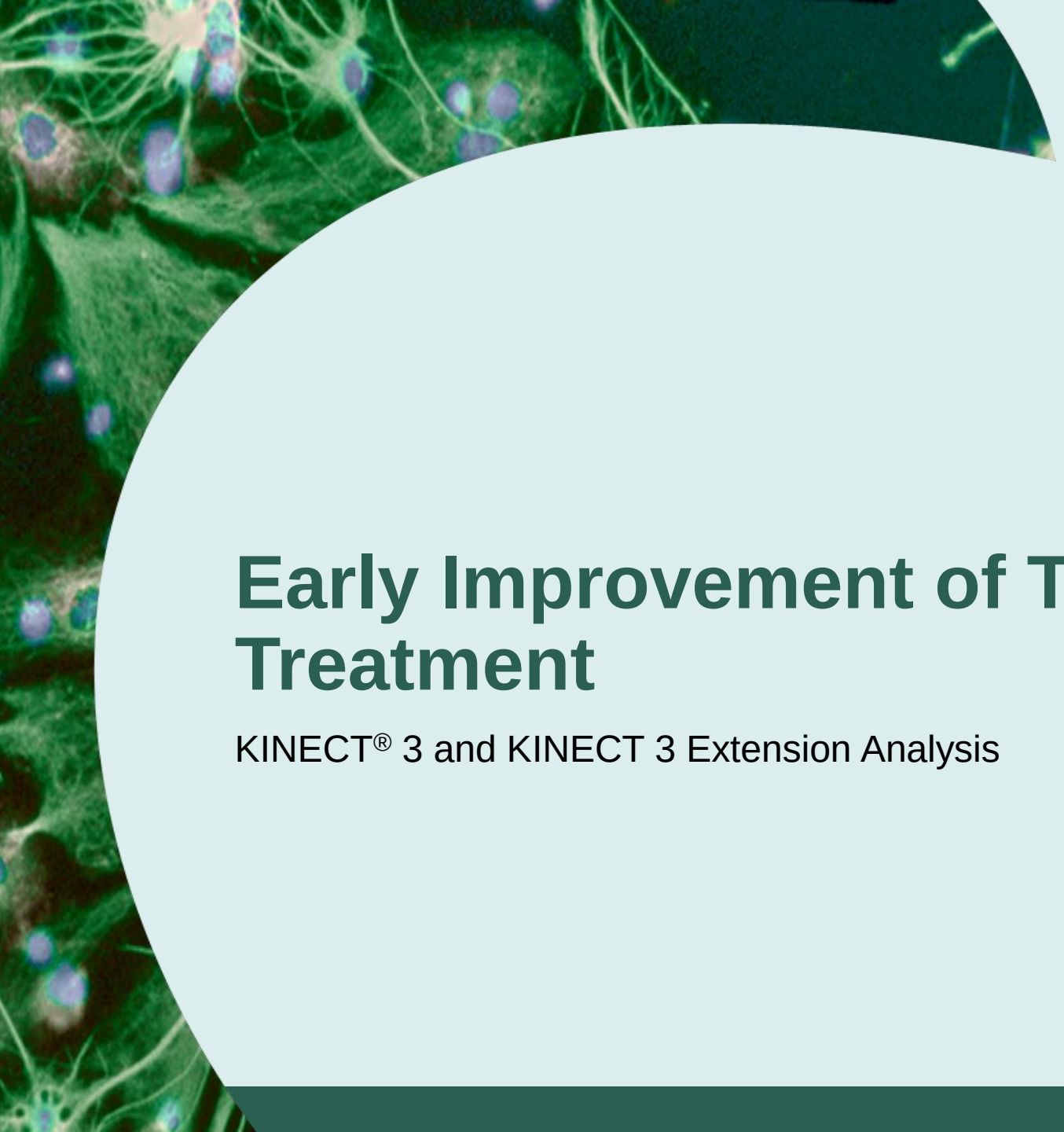
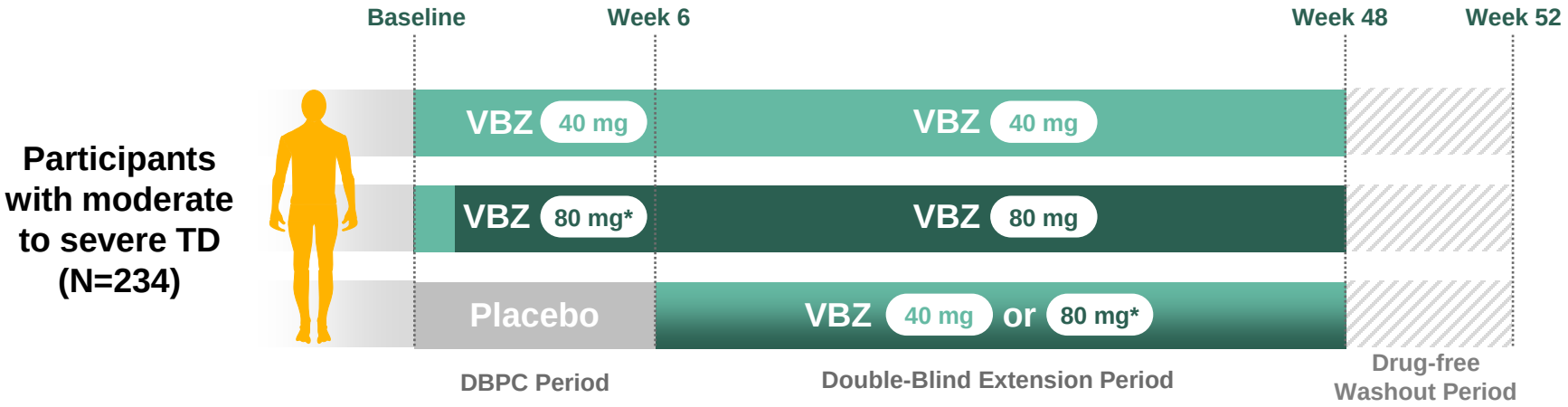


Early Improvement of TD with Valbenazine Treatment

KINECT® 3 and KINECT 3 Extension Analysis

KINECT 3 – Early Improvement Analysis: Study Design[1,2]



*Dosing started at 40 mg/day and increased to 80 mg/day after the first week

- KINECT 3 was a 6-week, randomized, double-blind, placebo-controlled (DBPC) Phase 3 study to assess the efficacy, safety, and tolerability of valbenazine in the treatment of TD
- Participants who completed the DBPC period in KINECT 3 continued to an extension period of 42 weeks of double-blind treatment with valbenazine and a 4-week drug-free period
- Data were analyzed from participants who were initially randomized to valbenazine (40 or 80 mg) and continued receiving valbenazine during the extension phase
  - Participants who were originally randomized to placebo were not included for this analysis

Detailed Study Design
Key Eligibility Criteria
Baseline Characteristics

DBPC, double-blinded placebo-controlled; TD, tardive dyskinesia; VBZ, valbenazine.

1. Hauser RA et al. *Am J Psych.* 2017. doi:10.1176/appi.ajp.2017.16091037; 2. Factor SA et al. *J Clin Pysch 2017*. https://doi.org/10.4088/JCP.17m11777

KINECT 3 – Early Improvement Analysis: Assessments

- Data from KINECT 3 were analyzed post-hoc to assess the long-term outcomes of valbenazine on TD using AIMS in participants who had early improvement based on self report (PGIC) or clinician judgement (CGI-TD)
- As scored by blinded central video raters, long-term outcomes included:
  - Mean change from baseline in AIMS total dyskinesia score (sum of items 1-7)
  - AIMS response (≥50% total score improvement from baseline) at Week 48
- AIMS outcomes were assessed in participants who reached an “early improvement” threshold at Week 2 (first post-baseline visit) of the DBPC period

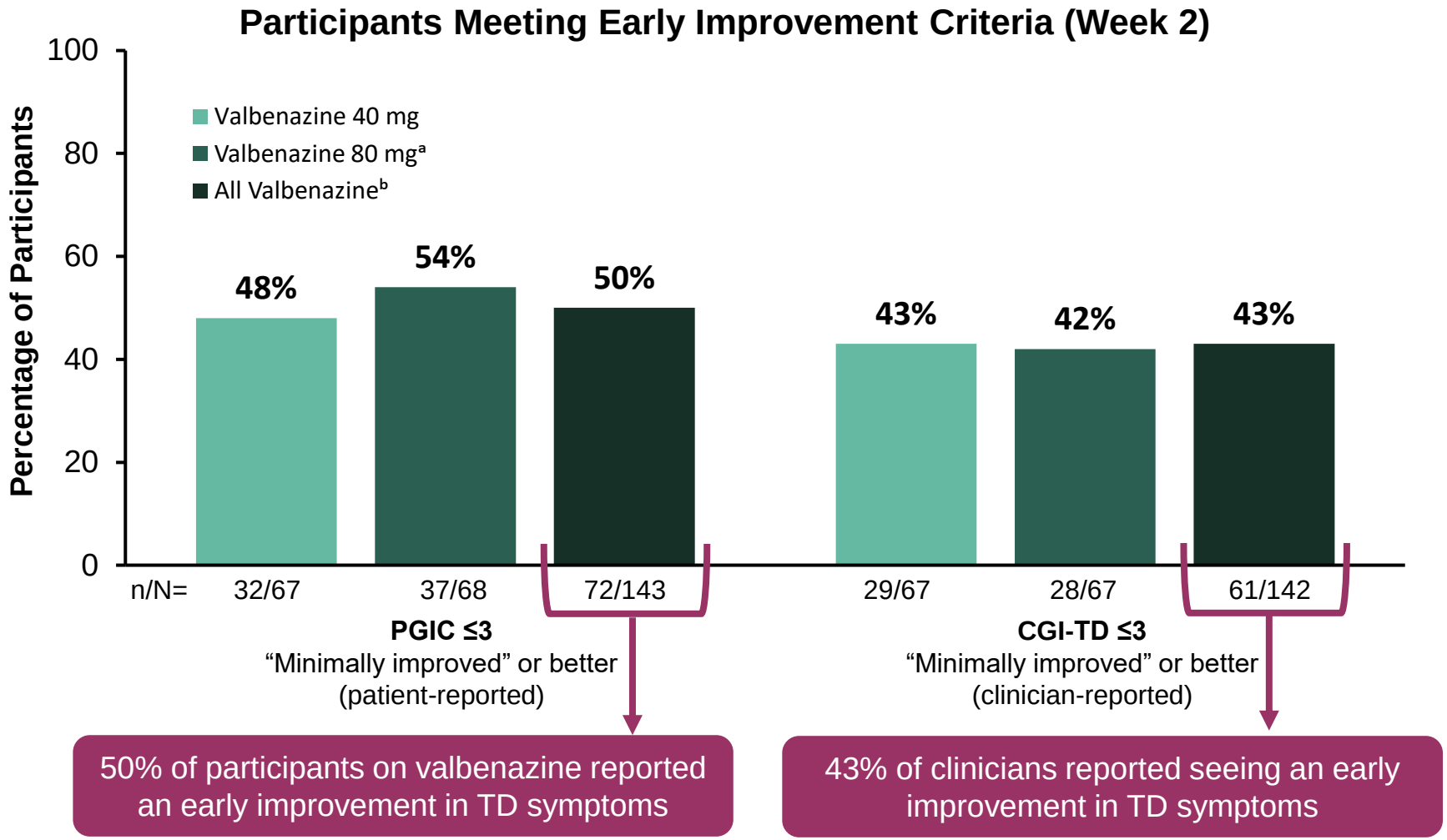
Score	PGIC or CGI-TD
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Worse
6	Much worse
7	Very much worse

→ Early Improvement

AIMS, abnormal involuntary movement scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; DBPC, double-blind placebo-controlled; PGIC, Patient Global Impression of Change; TD, tardive dyskinesia.

Factor SA, et al. MDS 2019; Nice, France.

KINECT 3 – Early Improvement Analysis: Participant and Clinician Assessments at Week 2

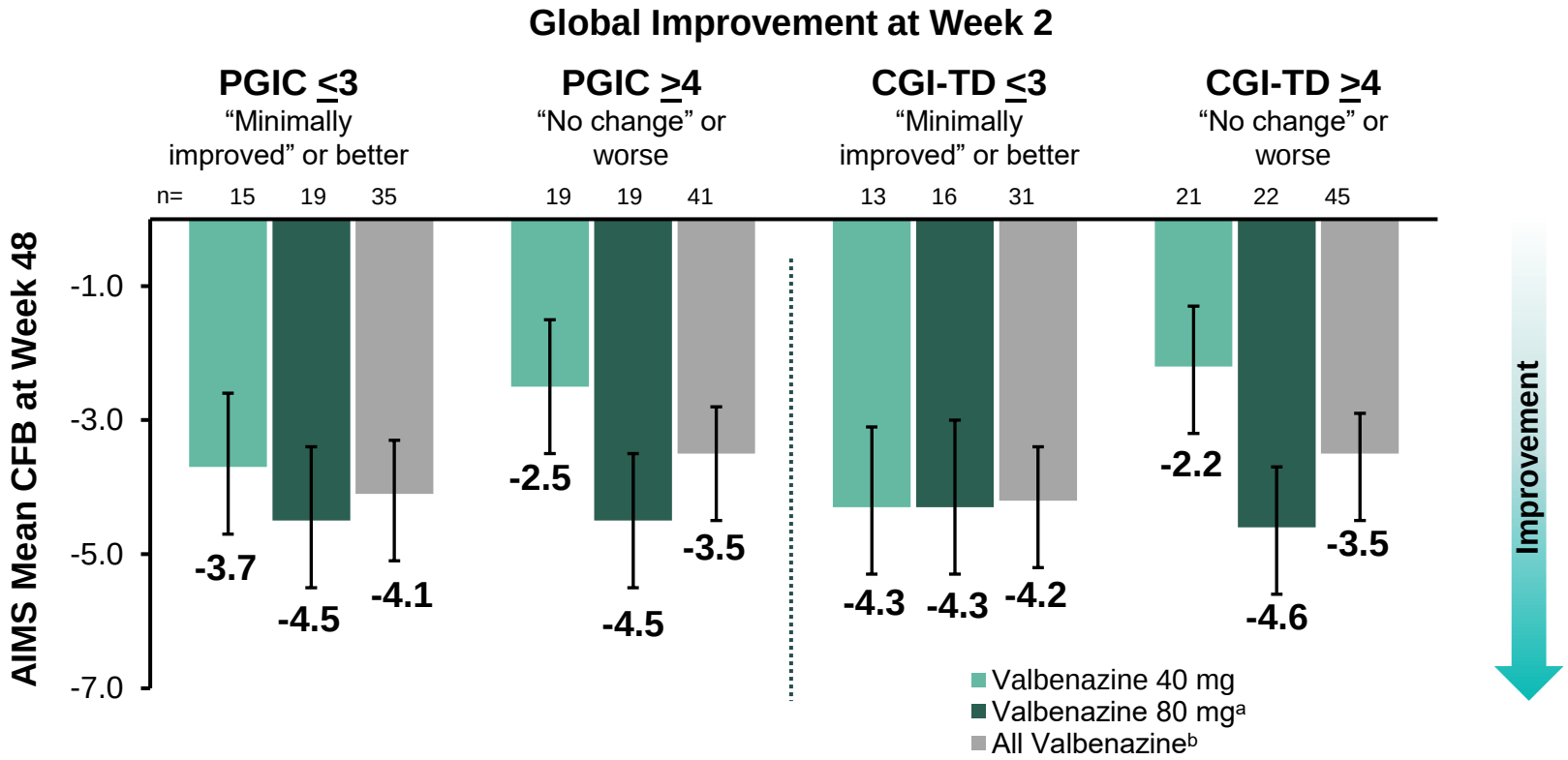


[a]Includes participants who remained at 80 mg with no dose reductions. [b]Includes participants who had a dose reduction from 80 mg to 40 mg after Week 4.
CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change; TD, tardive dyskinesia.

Factor SA, et al. MDS 2019; Nice, France.

KINECT 3 – Early Improvement Analysis: AIMS Total Score Mean Change at Week 48

- After 48 weeks of treatment, mean AIMS total score changes from baseline in participants with early PGIC and CGI-TD improvement were similar to those who did not reach the early improvement thresholds

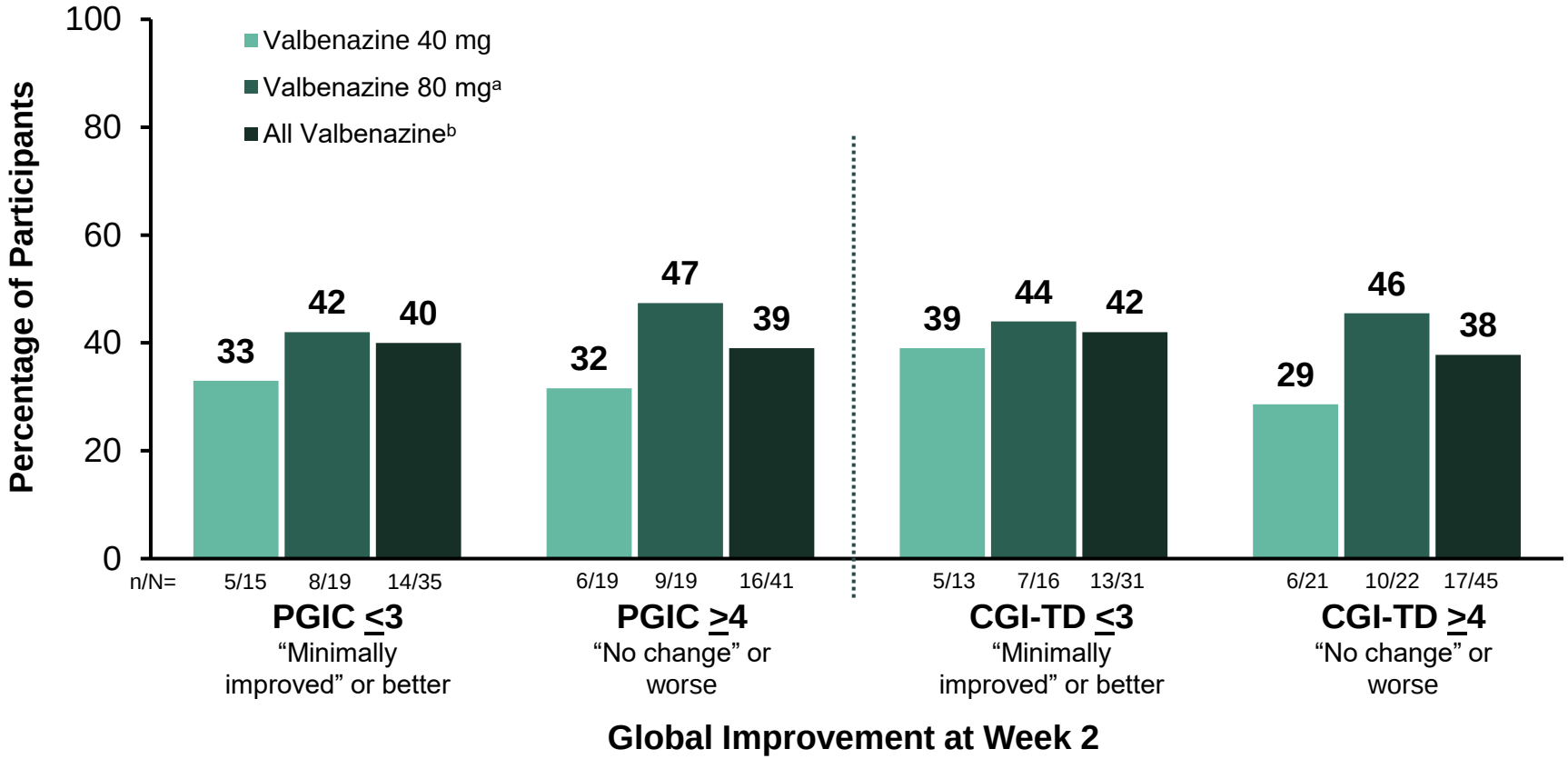


[a]Includes participants who remained at 80 mg with no dose reductions. [b]Includes participants who had a dose reduction from 80 mg to 40 mg after Week 4.
AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change.

Factor SA, et al. MDS 2019; Nice, France

KINECT 3 – Early Improvement Analysis: AIMS ≥50% Response at Week 48

- Similarly, AIMS response at Week 48 was similar in those who achieved early PGIC or CGI-TD improvement compared to those who did not achieve early PGIC or CGI-TD improvement



[a]Includes participants who remained at 80 mg with no dose reductions. [b]Includes participants who had a dose reduction from 80 mg to 40 mg after Week 4.
AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change.

Factor SA, et al. MDS 2019; Nice, France.

KINECT 3 – Early Improvement Analysis: Summary

- Based on patient- and clinician-reported global assessments that may take factors beyond movement severity into consideration, many participants in the KINECT 3 Extension study reached the early response threshold at Week 2
  - PGIC ≤3 (“minimally improved” or better): 50% of participants on valbenazine (72/143)
  - CGI-TD ≤3 (“minimally improved” or better): 43% of participants on valbenazine (61/142)
- After 48 weeks of treatment, mean AIMS total score changes from baseline in participants with early PGIC and CGI-TD improvements were similar to those who did not reach early improvement thresholds
- The most common adverse events (≥5% and >placebo) were somnolence
- Non-improvement based on subjective measures may not be predictive of long-term treatment outcomes

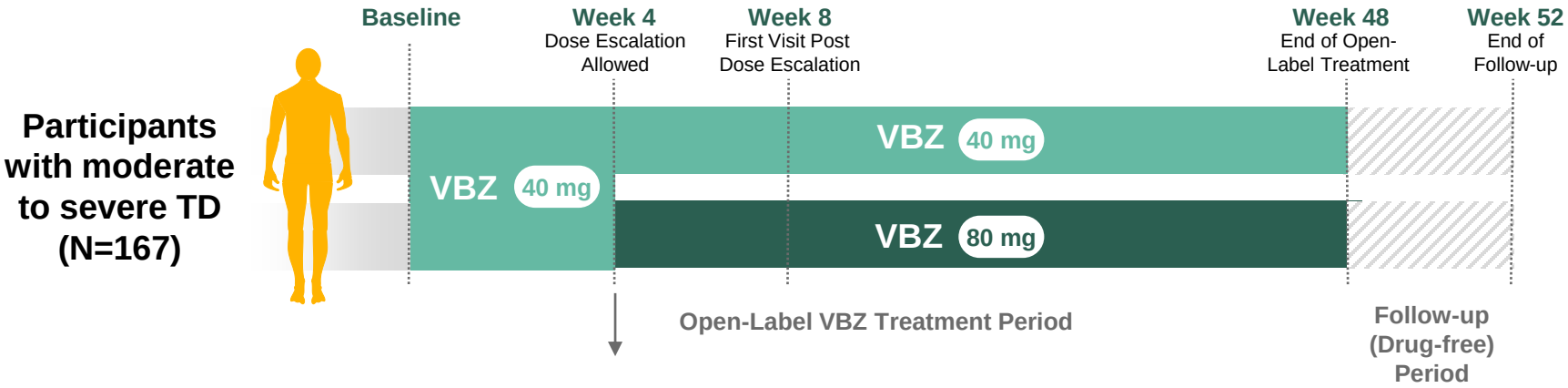
AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change.

Factor SA, et al. MDS 2019; Nice, France.

Patterns of TD Improvement Over Time

KINECT® 4

KINECT 4 – Treatment Response Patterns: Study Design



Participants could be escalated to 80 mg if they had a CGI-TD score of ≥3 and acceptable safety/tolerability with 40 mg, based on investigator judgement

- KINECT 4 was an open-label, long-term study investigating the safety and tolerability of valbenazine (40 or 80 mg/day) in adults with TD
- Data from study participants who received the study drug and had ≥1 post-baseline AIMS assessment were analyzed descriptively in a post-hoc analysis to characterize different patterns of TD improvement (N=158)

Detailed Study Design

Key Eligibility Criteria

Baseline Characteristics

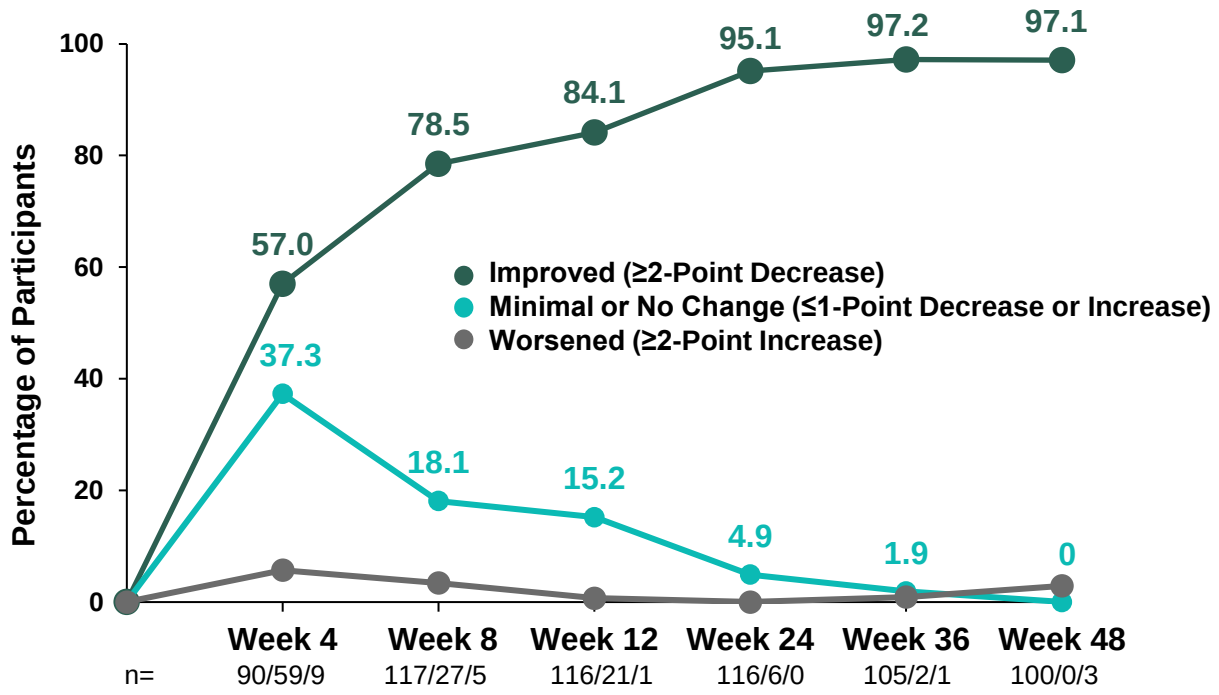
Patients who received 80 mg in the KINECT 4 study followed a different dosing schedule than those in the KINECT 3 pivotal study. In KINECT 3, patients had a dose increase from 40 to 80 mg after Week 1. In KINECT 4, patients had a dose increase from 40 to 80 mg after Week 4. The impact of this on long-term effectiveness is not known.
AIMS, Abnormal Involuntary Movement Scale; TD, tardive dyskinesia; VBZ, valbenazine.

Correll CU, et al. APA 2021.

KINECT 4 – Treatment Response Patterns: AIMS MCID Assessment[1]

AIMS Total Score Changes with Long-Term Valbenazine Treatment

- Based on the MCID for AIMS total score[2], the proportion of participants with a ≥2-point decrease (improvement) or increase (worsening) were analyzed by study visit
- The percentage of participants with a clinically meaningful improvement in AIMS total score increased over time, with ≥95% having a clinically meaningful improvement at Weeks 24, 36, and 48



AIMS, Abnormal Involuntary Movement Scale; MCID, minimal clinically important difference; n, number of available assessments for improved/minimal or no change/worsened.

1. Correll CU, et al. APA 2021. 2. Stacy M, Sajatovic M, Kane JM, et al. Mov Disord. 2019;34:1203-9.

KINECT 4 – Treatment Response Patterns: AIMS Response Assessment[1]

Definition of Response Categories

- Based on the MCID for clinically meaningful response[2] and protocol-defined response (≥30% and ≥50% AIMS total score improvement from baseline, respectively), participants were categorized as follows:

Response Categories	Study Week					
	4	8	12	24	36	48 (or last visit)
Early/Strong/Sustained	✓	✓	✓	✓	✓	✓
Early/Sustained	✓	✓	✓	✓	✓	✓
Early	✓					✓
Delayed		✓				✓
Late[a]			✓			✓
Poor/No response						

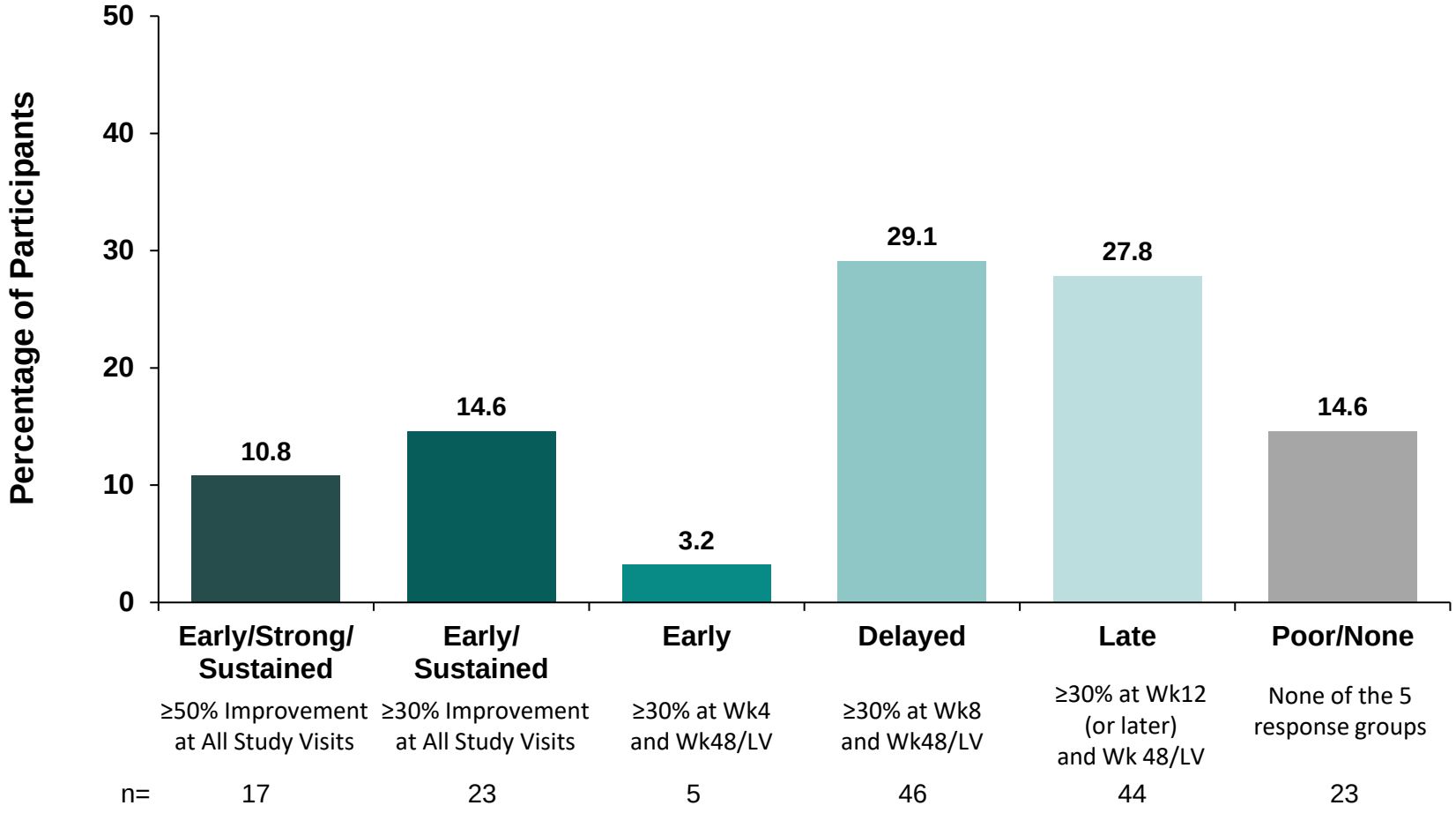
✓ ≥50% Improvement ✓ ≥30% Improvement

[a]Week 12 or later
AIMS, Abnormal Involuntary Movement Scale; MCID, minimal clinically important difference.

1. Correll CU, et al. APA 2021. 2. Stacy M, Sajatovic M, Kane JM, et al. Mov Disord. 2019;34:1203-9.

KINECT 4 – Treatment Response Patterns: AIMS Response Assessment

AIMS Response Patterns Across 48 Weeks of Valbenazine Treatment



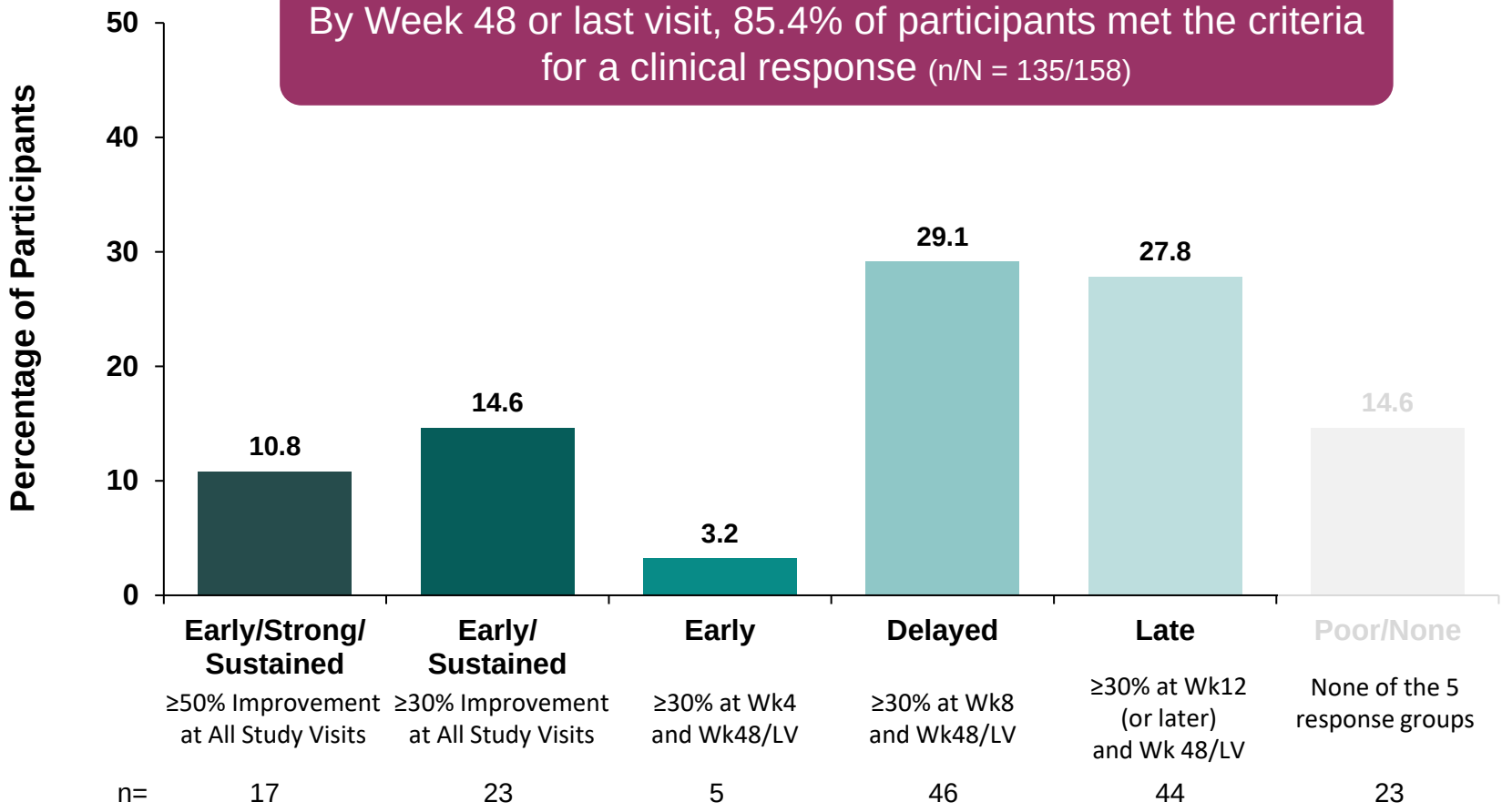
AIMS, Abnormal Involuntary Movement Scale; LV, last visit; Wk, week.

Correll CU, et al. APA 2021.

KINECT 4 – Treatment Response Patterns: AIMS Response Assessment

AIMS Response Patterns Across 48 Weeks of Valbenazine Treatment

By Week 48 or last visit, 85.4% of participants met the criteria for a clinical response (n/N = 135/158)

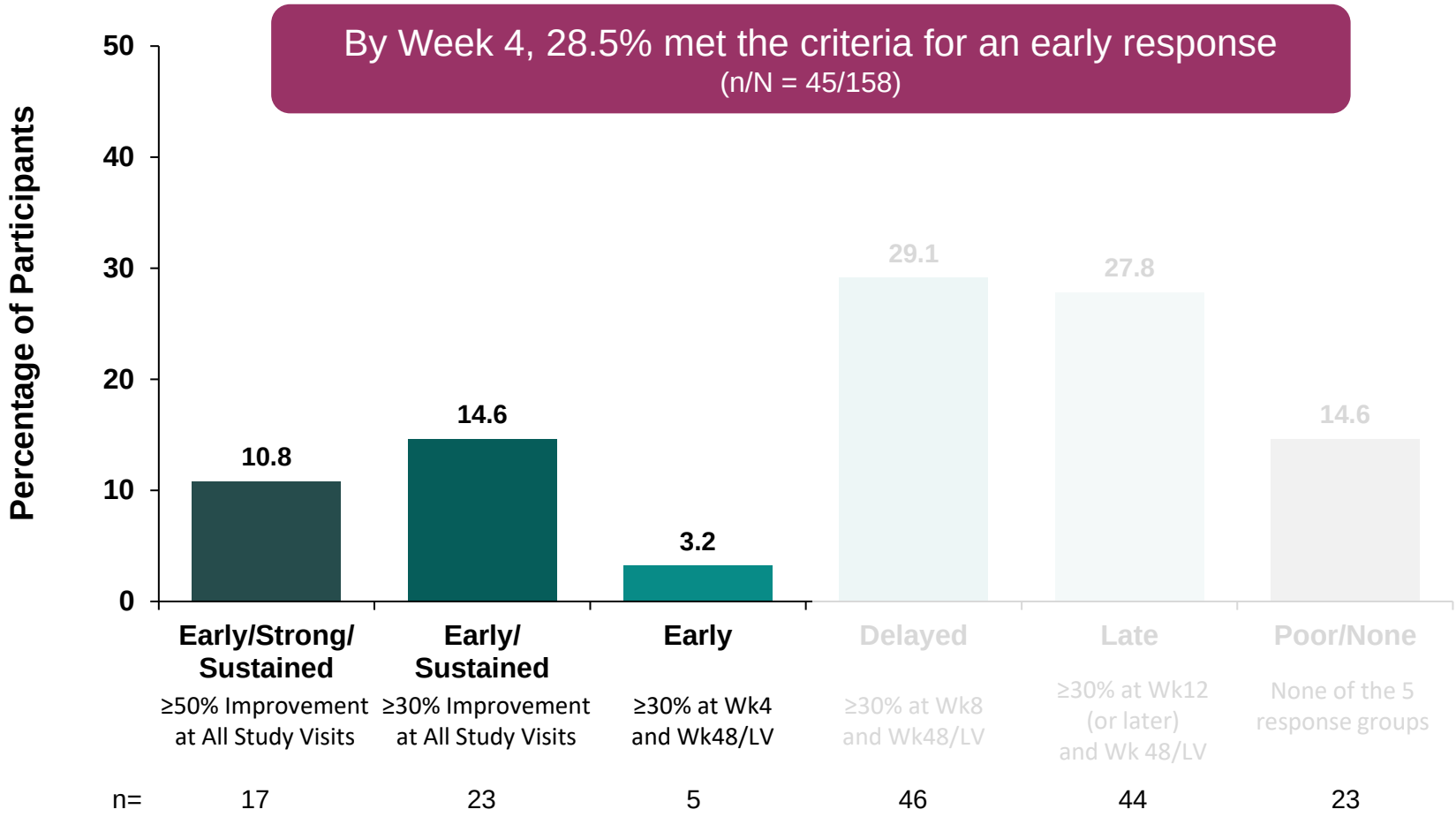


AIMS, Abnormal Involuntary Movement Scale; LV, last visit; Wk, week.

Correll CU, et al. APA 2021.

KINECT 4 – Treatment Response Patterns: AIMS Response Assessment

AIMS Response Patterns Across 48 Weeks of Valbenazine Treatment



AIMS, Abnormal Involuntary Movement Scale; LV, last visit; Wk, week.

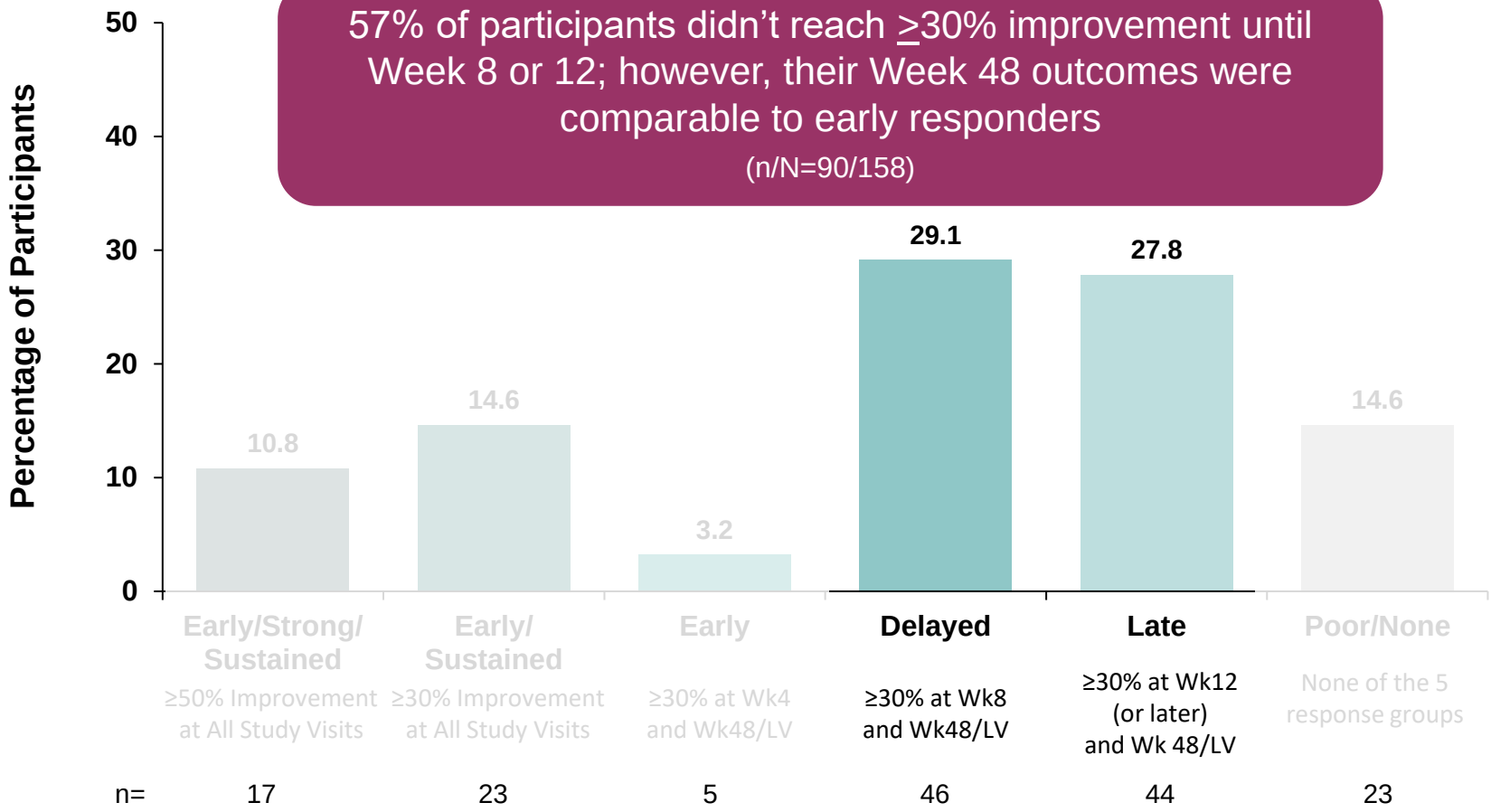
Correll CU, et al. APA 2021.

KINECT 4 – Treatment Response Patterns: AIMS Response Assessment

AIMS Response Patterns Across 48 Weeks of Valbenazine Treatment

57% of participants didn't reach ≥30% improvement until Week 8 or 12; however, their Week 48 outcomes were comparable to early responders

(n/N=90/158)

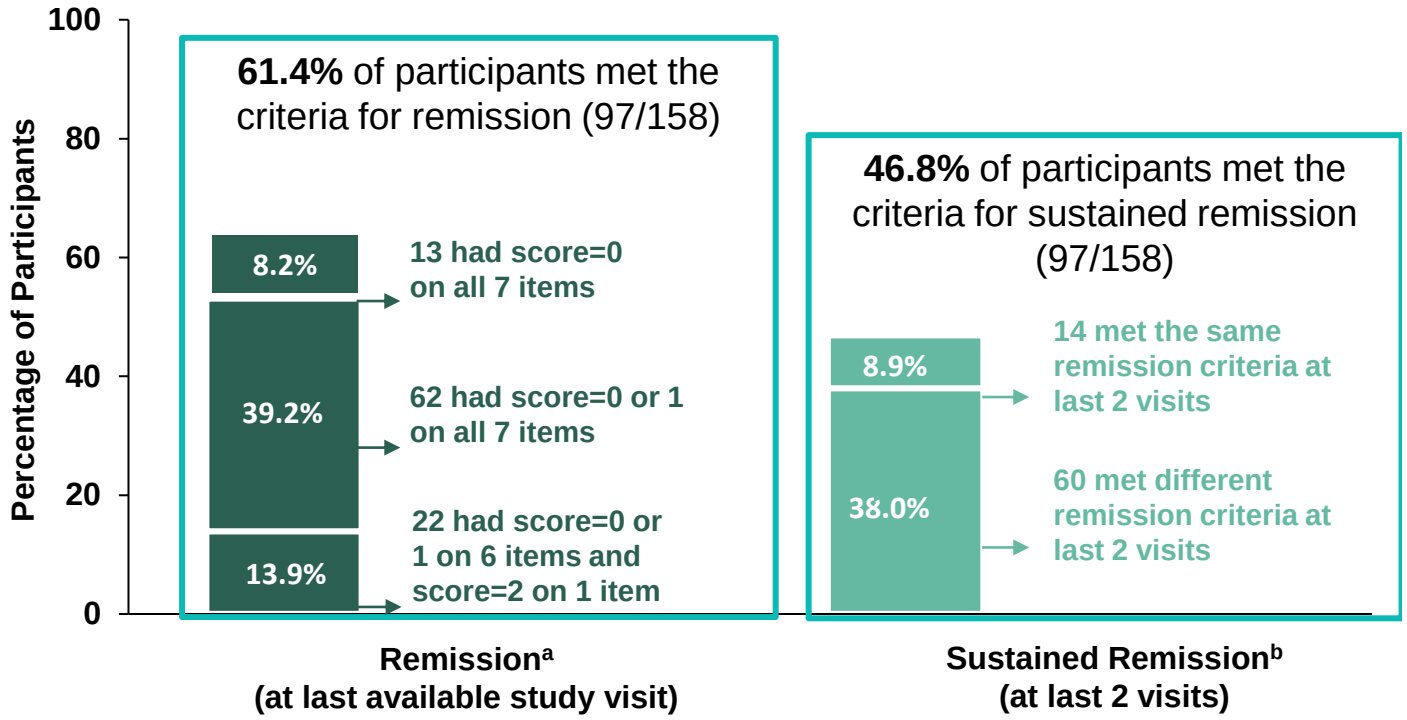


AIMS, Abnormal Involuntary Movement Scale; LV, last visit; Wk, week.

Correll CU, et al. APA 2021.

KINECT 4 – Treatment Response Patterns: Remission and Sustained Remission Assessment[1]

- Based on Schooler-Kane criteria for TD,[2] remission was defined as absence of TD (i.e., score of 2 [“mild”] in ≤1 AIMS item and all other item scores ≤1)
  - Sustained remission was defined as meeting remission definition at last 2 visits



[a]The numbers are presented for participants with each possible score combination.
[b]The numbers are presented for participants who met the same remission criteria for the last 2 visits or different criteria at the last 2 visits (e.g., score=1 on several items and then score=0 on all 7 items). Results include participants who had only 1 post-baseline AIMS assessment (categorized as having no sustained remission)
AIMS, Abnormal Involuntary Movement Scale; TD, tardive dyskinesia.

1. Correll CU, et al. APA 2021. 2. Schooler NR, Kane JM. *Arch Gen* Psychiatry. 1982;39:486-7.

KINECT 4 – Treatment Response Patterns: Summary

- Patterns of improvement may vary, but sustained clinically meaningful or robust responses (≥30% or ≥50% AIMS total score decrease) were observed with once-daily valbenazine in this KINECT 4 post-hoc analysis[1]
  - 85.4% (135/158) of participants met criteria for a response at Week 48
- 61.4% and 46.8% of participants met the criteria for remission[a] and sustained remission[b], respectively[1]
- In the KINECT 4 study, the most common TEAEs were urinary tract infection (8.5%) and headache (5.2%) in all participants taking valbenazine (40 mg and 80 mg)[2]

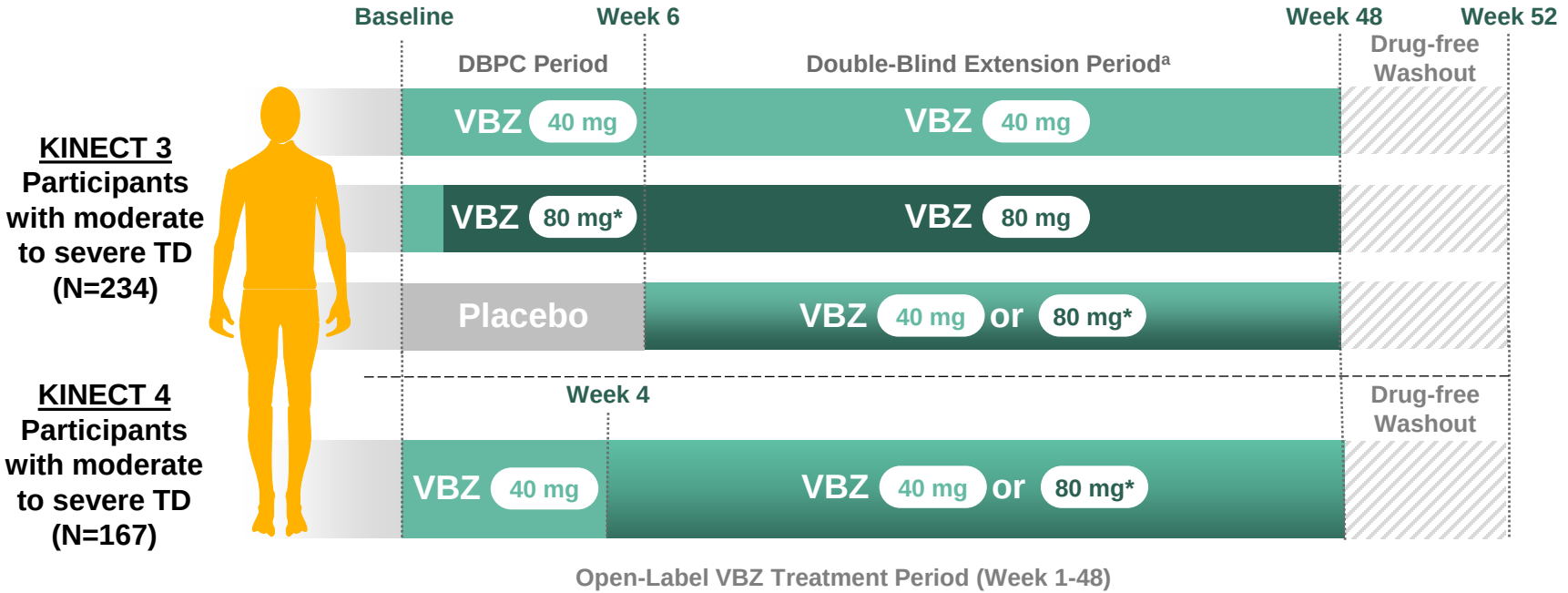
[a]Remission defined as score of 2 [“mild”] in ≤1 AIMS item and all other item scores ≤1 at last available study visit.
[b]Sustained remission defined as meeting a remission definition at last 2 visits.
AIMS, Abnormal Involuntary Movement Scale; TEAE, treatment-emergent adverse event.

1. Correll CU, et al. APA 2021. 2. Marder SR, et al. *J Clin Psychopharmacology*. 2019;39(6):620-627.

Durability of Response

KINECT® 3 & 4

KINECT 3&4 – Durability of Response: Study Design



- Data from Week 48 (end of treatment) and Week 52 (end of washout) of KINECT 3 and KINECT 4 were pooled to assess the percentage of participants who maintained various levels of response after medication washout
  - Available Week 48/52 data from KINECT 3 and KINECT 4 were pooled by dose group (valbenazine 40 mg & 80 mg)
  - Participants who received placebo in the double-blind, placebo-controlled phase of KINECT 3 were excluded from analyses

[a]All KINECT 3 participants randomized to valbenazine 80mg in the DBPC period or re-randomized from placebo to valbenazine 80mg in the extension period were initiated at 40 mg for 1 week
*Includes participants who had a dose reduction to 40 mg due to tolerability issues
DBPC, double-blind, placebo-controlled; TD, tardive dyskinesia; VBZ, valbenazine.

Caroff SN, et al. ACNP 2019; Orlando, FL.

KINECT 3&4 – Durability of Response: Assessments

- Descriptive analyses were conducted in participants with available assessments at both Week 48 and Week 52 (40 mg, n=54; 80 mg, n=124):
  - AIMS total score (sum of items 1-7) as assessed by blinded central video raters (KINECT 3) or site investigators (KINECT 4)
  - CGI-TD as assessed by site investigators
  - PGIC self-reported by study participants

	Week 48 Responder Requirements		Week 52 Responder Requirements
AIMS Total score	≥50% improvement from baseline (“robust” response)	AND	≥50%, ≥40%, ≥30%, ≥20%, ≥10%
	≥30% improvement from baseline (“clinically meaningful” response)	AND	≥30%, ≥20%, ≥10%
CGI-TD score	≤2 (“much improved” or better)	AND	≤2, ≤3
	≤3 (“minimally improved” or better)	AND	≤3
PGIC score	≤2 (“much improved” or better)	AND	≤2, ≤3
	≤3 (“minimally improved” or better)	AND	≤3

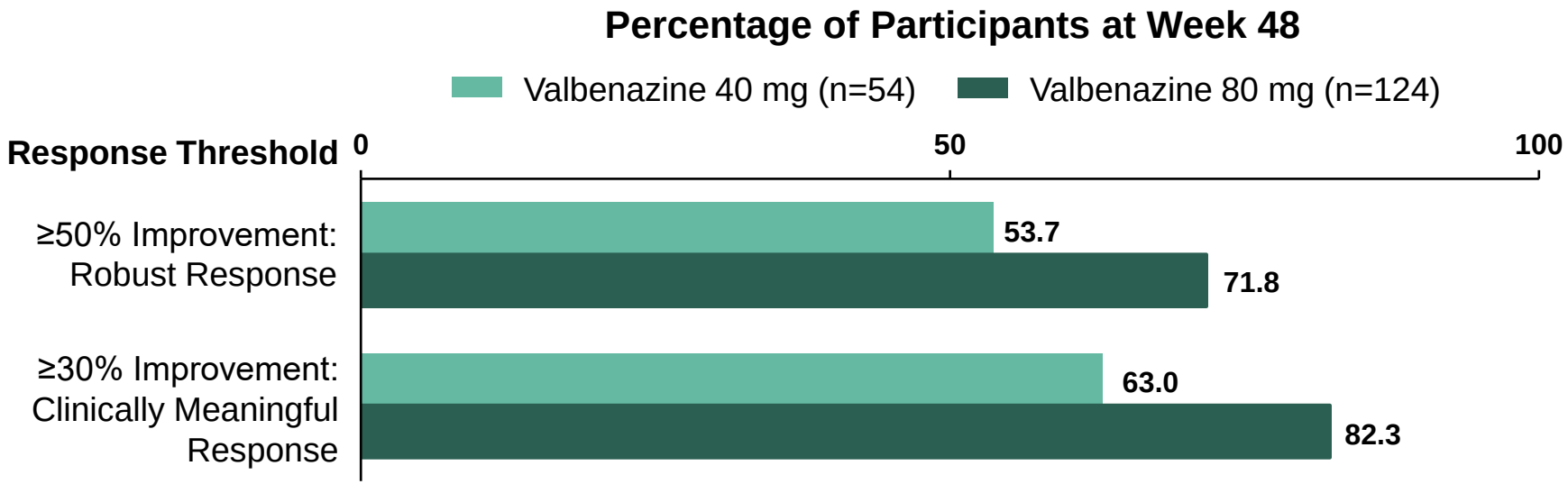
Week 48/52 Responder Requirements

AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change.

Caroff SN, et al. ACNP 2019; Orlando, FL.

KINECT 3&4 – Durability of Response: Robust and Clinically Meaningful AIMS Response at Week 48

- At Week 48 (end of treatment), a majority of participants met the threshold for a robust AIMS response (≥50% total score improvement) or a clinically meaningful AIMS response (≥30% total score improvement)

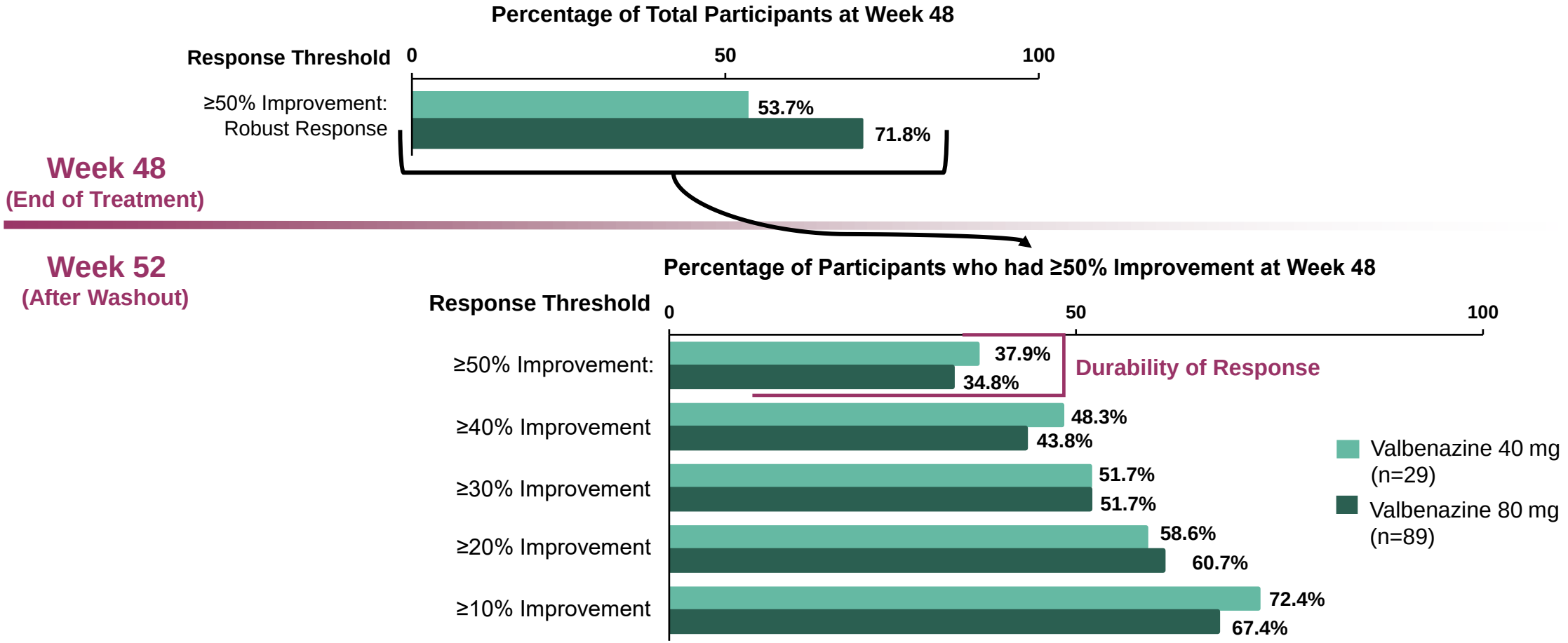


AIMS, Abnormal Involuntary Movement Scale.

Caroff SN, et al. ACNP 2019; Orlando, FL.

KINECT 3&4 – Durability of Response: Robust and Durable Response at Week 52

- More than 30% of participants with a robust AIMS response at Week 48 maintained the same level of improvement at Week 52

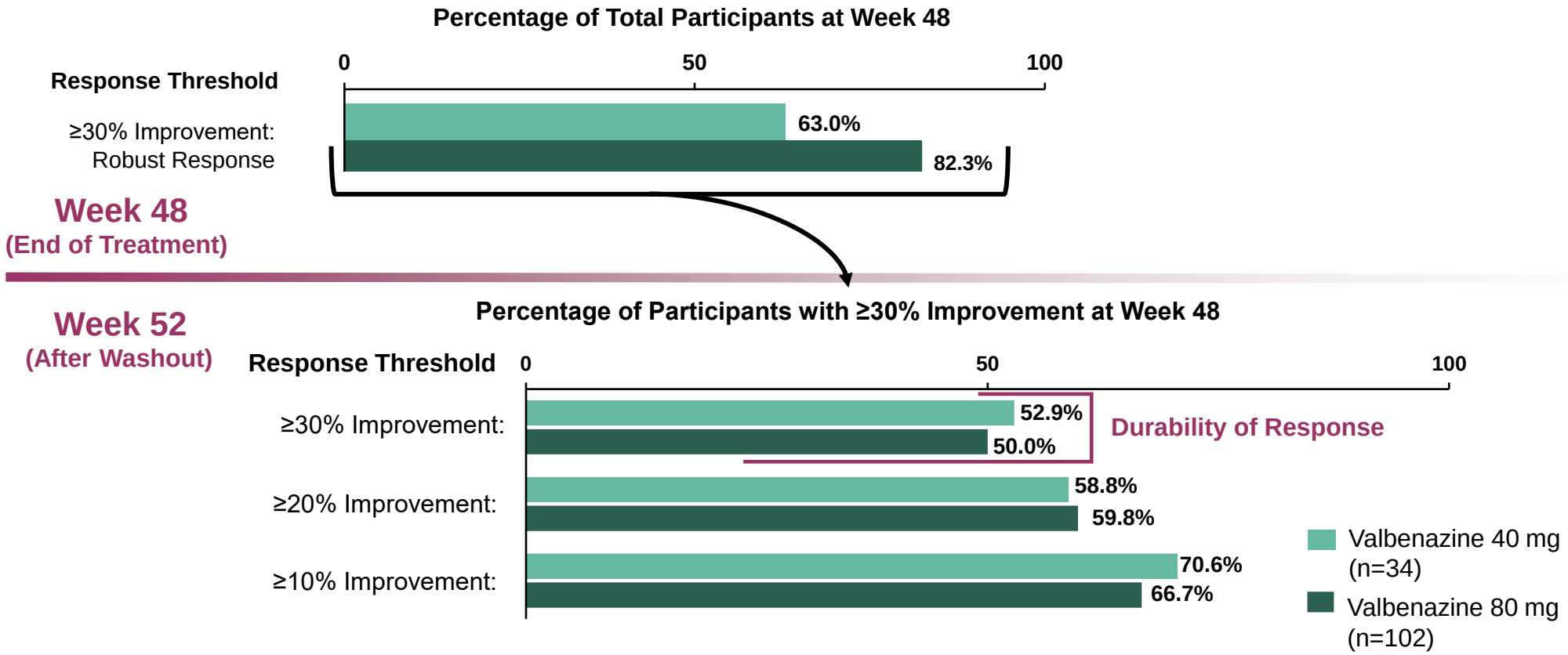


AIMS, Abnormal Involuntary Movement Scale.

Caroff SN, et al. ACNP 2019; Orlando, FL.

KINECT 3&4 – Durability of Response: Clinically Meaningful and Durable Response at Week 52

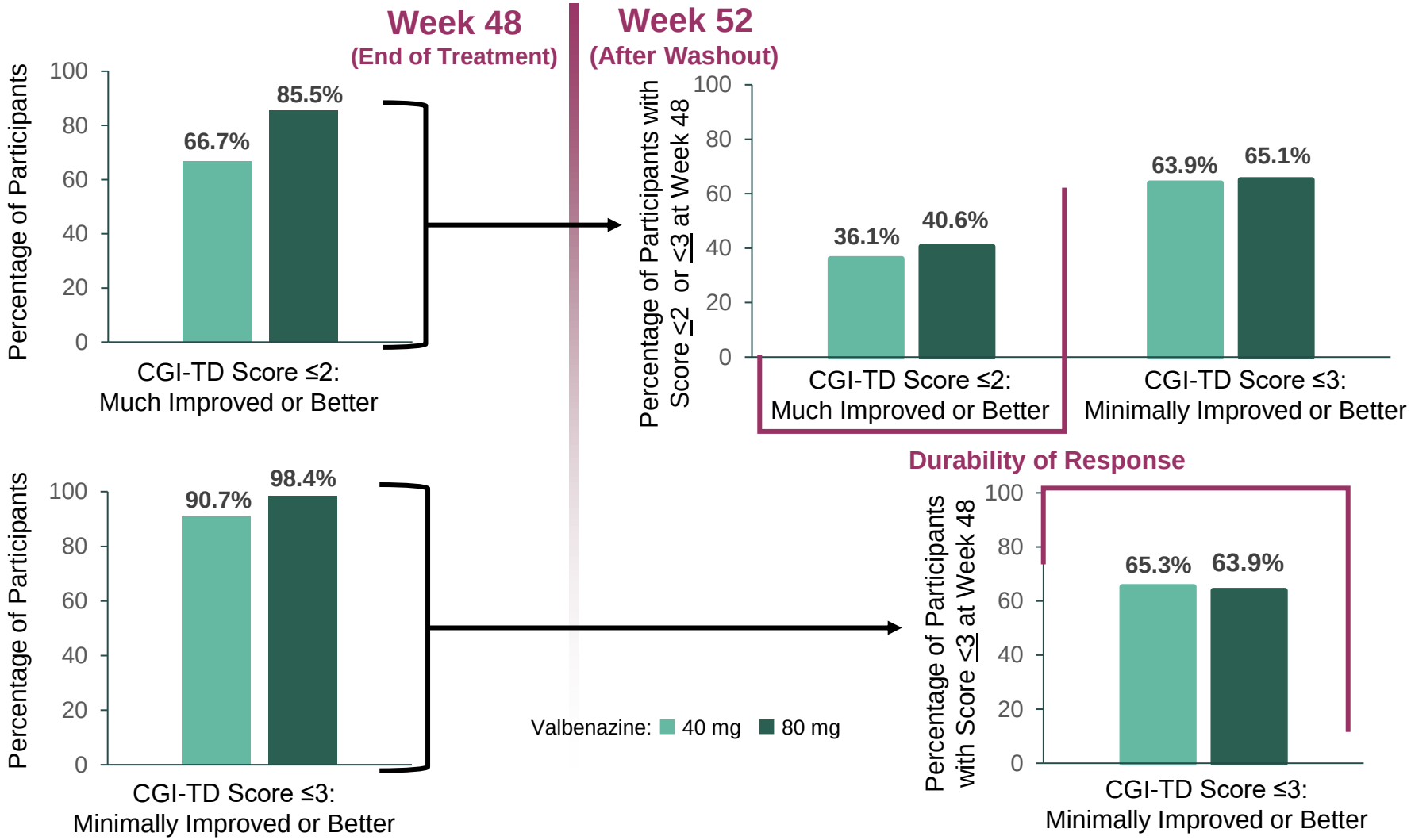
- More than 50% of the participants who had a clinically meaningful AIMS response at Week 48 maintained the same level of improvement at Week 52



AIMS, Abnormal Involuntary Movement Scale.

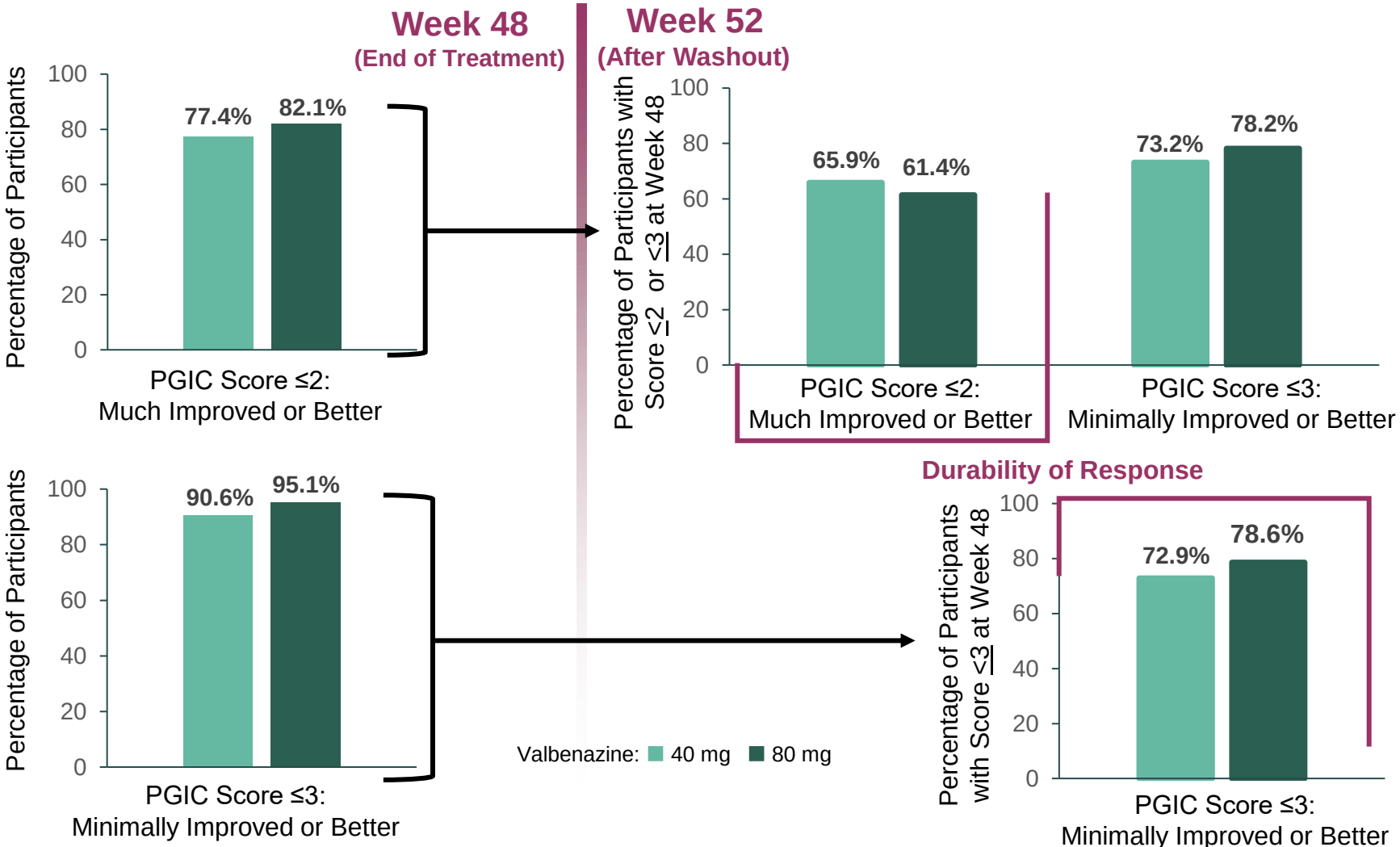
Caroff SN, et al. ACNP 2019; Orlando, FL.

KINECT 3&4 – Durability of Response: CGI-TD Response at Weeks 48 and 52



Week 48: 40 mg (n=54), 80 mg (124); Week 48 Score ≤2 -> Week 52: 40 mg (n=36), 80 mg (n=106); Week 48 Score ≤3 -> Week 52: 40 mg (n=49), 80 mg (n=122).
CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia.
Caroff SN, et al. ACNP 2019; Orlando, FL.

KINECT 3&4 – Durability of Response: PGIC Response at Weeks 48 and 52



[a]One participant did not have a PGIC assessment at both Week 48 and Week 52
Week 48: 40 mg (n=53), 80 mg (123); Week 48 Score ≤2 -> Week 52: 40 mg (n=41), 80 mg (n=101); Week 48 Score ≤3 -> Week 52: 40 mg (n=48), 80 mg (n=117).
PGIC, Patient Global Impression of Change.
Caroff SN, et al. ACNP 2019; Orlando, FL.

KINECT 3&4 – Durability of Response: Summary

- In a post-hoc analysis of two long-term studies of valbenazine in adults with TD (KINECT 3 & KINECT 4) response and durability of response after washout was assessed using AIMS, CGI-TD, PGIC
- More than 50% of participants who had had a clinically meaningful AIMS response (≥30% improvement from baseline) at Week 48 maintained the same level of improvement at Week 52[1]
  - Valbenazine 40mg, 52.9%; valbenazine 80mg, 50.0%
- More than 30% of participants with a robust AIMS response (≥50% improvement from baseline) at Week 48 maintained the same level of improvement at Week 52[1]
  - Valbenazine 40mg, 37.9%; valbenazine 80mg, 34.8%
- A majority of participants who were minimally improved or better at Week 48 (CGI-TD or PGIC score ≤3) maintained the same level of response at Week 52[1]
  - CGI-TD: VBZ 40mg, 65.3%; VBZ 80mg, 63.9%
  - PGIC: VBZ 40mg, 72.9%; VBZ 80mg, 78.6%
- Pooled long-term data from KINECT 3 and KINECT 4 studies showed that headache (8.9%[a]) and urinary tract infection (8.9%[a]) were the most commonly reported TEAEs in all participants taking VBZ (n= 304)[2]

[a]Reported in ≥5% of all participants in the long-term pooled population.

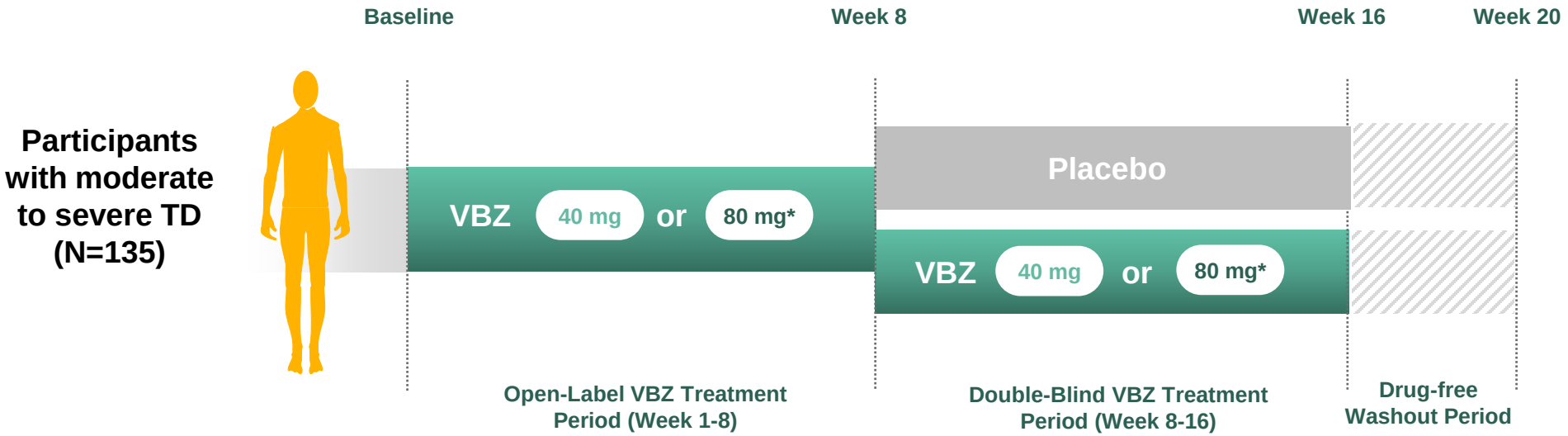
AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change; TEAE, Treatment-Emergent Adverse Event; TD, tardive dyskinesia; VBZ, valbenazine.

1. Caroff SN, et al. ACNP 2019; Orlando, FL; 2. Marder SR, et al. US Psych Congress 2018; Orlando, FL.

Impact of Treatment Withdrawal

Study 4002

Study 4002 – Randomized Withdrawal: Study Design



- A Phase 4, double-blind, placebo-controlled, withdrawal study was conducted to assess the persistence of valbenazine effect in patients with TD
- During the 8-week open-label treatment period, once-daily valbenazine was initiated at 40 mg and escalated to 80 mg after 1 week (dose reduction was allowed for tolerability)
- After 8 weeks of open-label valbenazine, participants were randomized (1:1) to receive 8 weeks of placebo (VBZ/PBO) or continue taking the same valbenazine dose (VBZ/VBZ group)

*During the open-label treatment period, all participants received 40 mg for 1 week followed by 80 mg for 7 weeks. At any time during the open-label or DBPC treatment periods, valbenazine dose reduction to 40 mg was allowed for tolerability. To maintain the blind, subjects receiving placebo continued to receive placebo.

DBPC, double-blind, placebo-controlled; PBO, placebo; TD, tardive dyskinesia; VBZ, valbenazine.

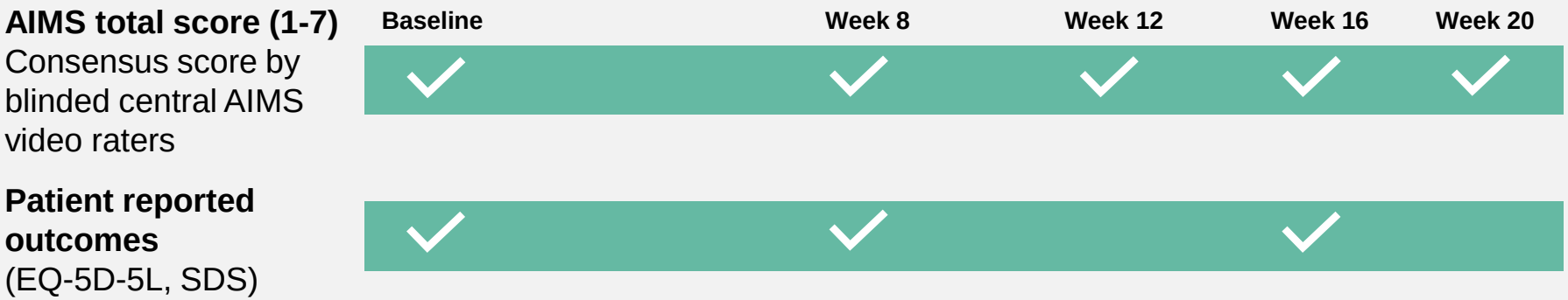
Jimenez R, et al. ISPOR EU 2021.

Baseline Characteristics

Key Eligibility Criteria

Study 4002 – Randomized Withdrawal: Assessments

- Descriptive analyses were conducted in participants with available assessments from baseline to Week 20 (end of study) based on AIMS total score and patient reported outcomes
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests, vital sign measurements, ECGs, BPRS, and the C-SSRS



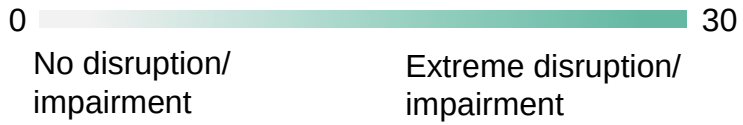
EQ-5D-5L:

Utility Index	0 to 1	"health state equivalent to death" to "perfect health"
Visual Analog Scale (VAS)	0 to 100	"worst imaginable health state" to "best imaginable health state"

SDS:

Measures disruption/functional impairment in 3 domains:

- Work/school
- Social life
- Family/home life



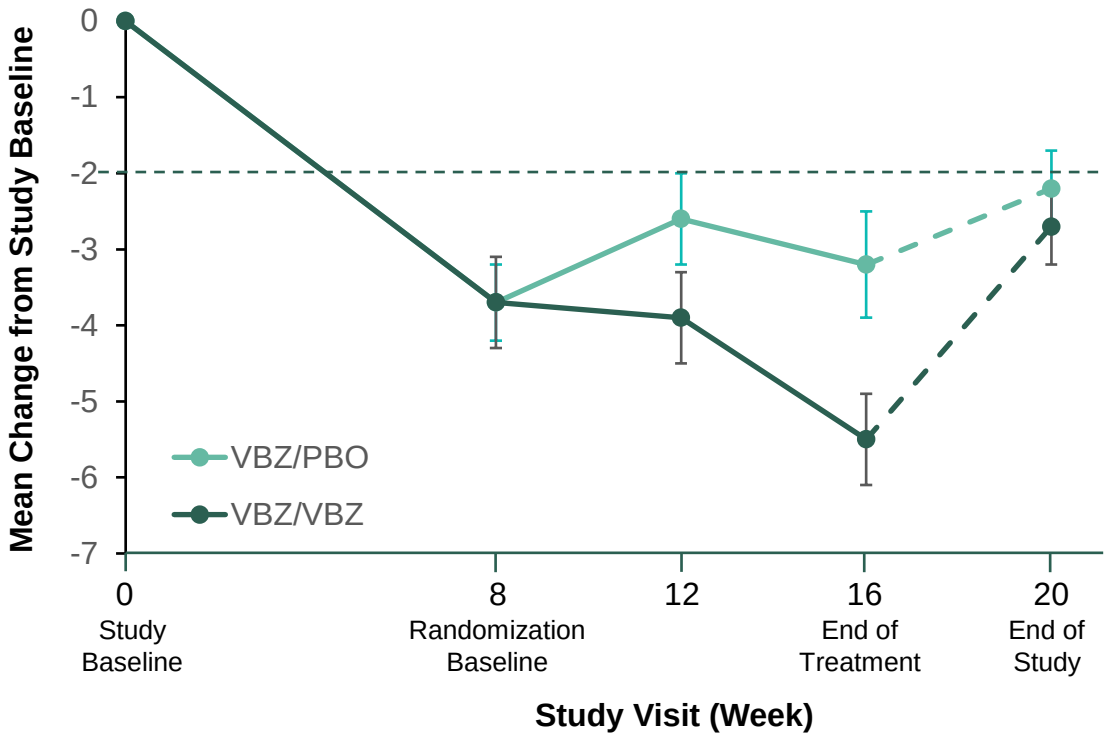
AIMS, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale; Columbia-Suicide Severity Rating Scale, C-SSRS; ECG, electrocardiogram; EQ-5D-5L, EuroQoL's 5-Dimension 5-Level questionnaire; SDS, Sheehan Disability Scale.

Jimenez R, et al. ISPOR EU 2021.

Study 4002 – Randomized Withdrawal: AIMS Total Score Change from Baseline

- Mean changes in AIMS total score from study baseline to Week 8 (end of open-label period) indicated improvements with valbenazine treatment: VBZ/PBO, -3.7±0.5; VBZ/VBZ, -3.7±0.6
- Changes from Week 8 (randomization baseline) to Week 16 (end of randomized withdrawal period) indicated initial loss of valbenazine effect after treatment withdrawal: VBZ/PBO, 0.7±0.7; VBZ/VBZ, -1.7±0.4
  - However, mean changes from study baseline to Week 16 suggested some overall persistence of valbenazine effect: VBZ/PBO, -3.2±0.7; VBZ/VBZ, -5.5±0.6

Study Visit	VBZ/PBO, n	VBZ/VBZ, n
Week 0	58	59
Week 8	58	59
Week 12	56	58
Week 16	53	56
Week 20	53	55



Dashed line indicates minimally clinically important difference (MCID, ≥2 AIMS total score change from study baseline).

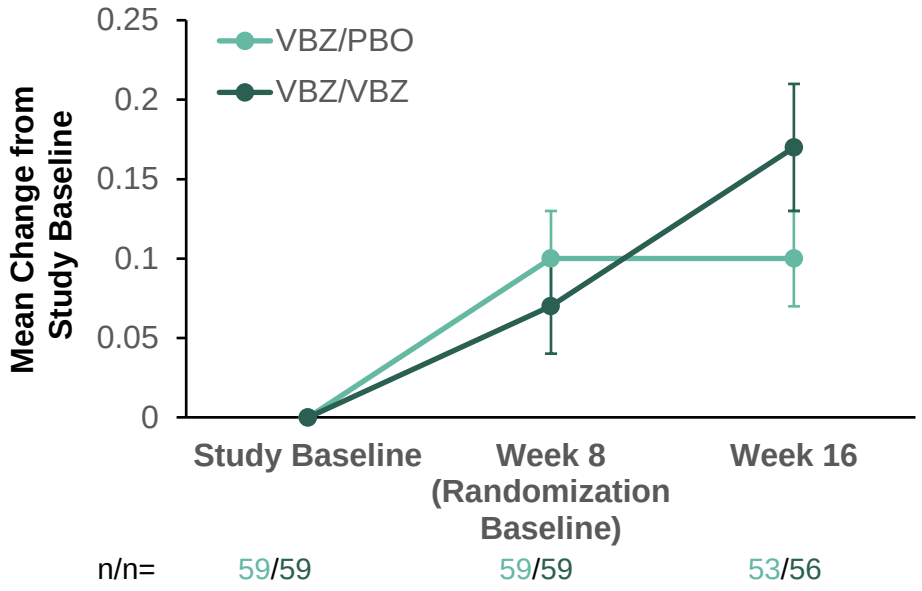
AIMS, Abnormal Involuntary Movement Scale; MCID, minimal clinically important difference; PBO, placebo; VBZ, valbenazine.

Jimenez R, et al. ISPOR EU 2021.

Study 4002 – Randomized Withdrawal: EQ-5D-5L Score Change from Baseline to Week 16

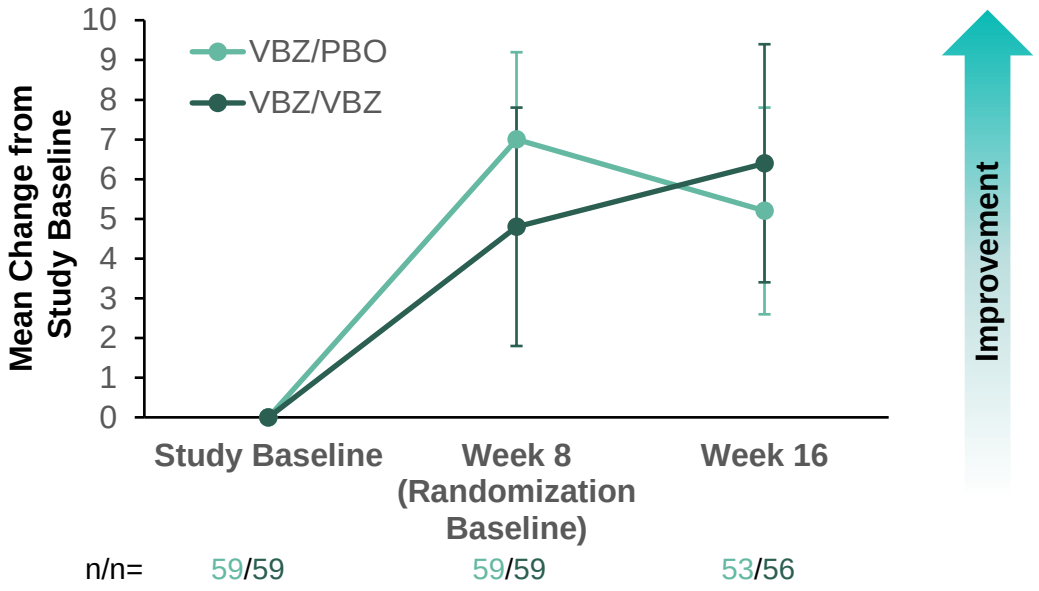
- Mean improvements from study baseline to Week 16 for healthy-related quality of life (EQ-5D-5L) was greater in patients who continued taking valbenazine

Utility Index Score:



Utility Index	0 to 1	"health state equivalent to death" to "perfect health"

Health State VAS Score:



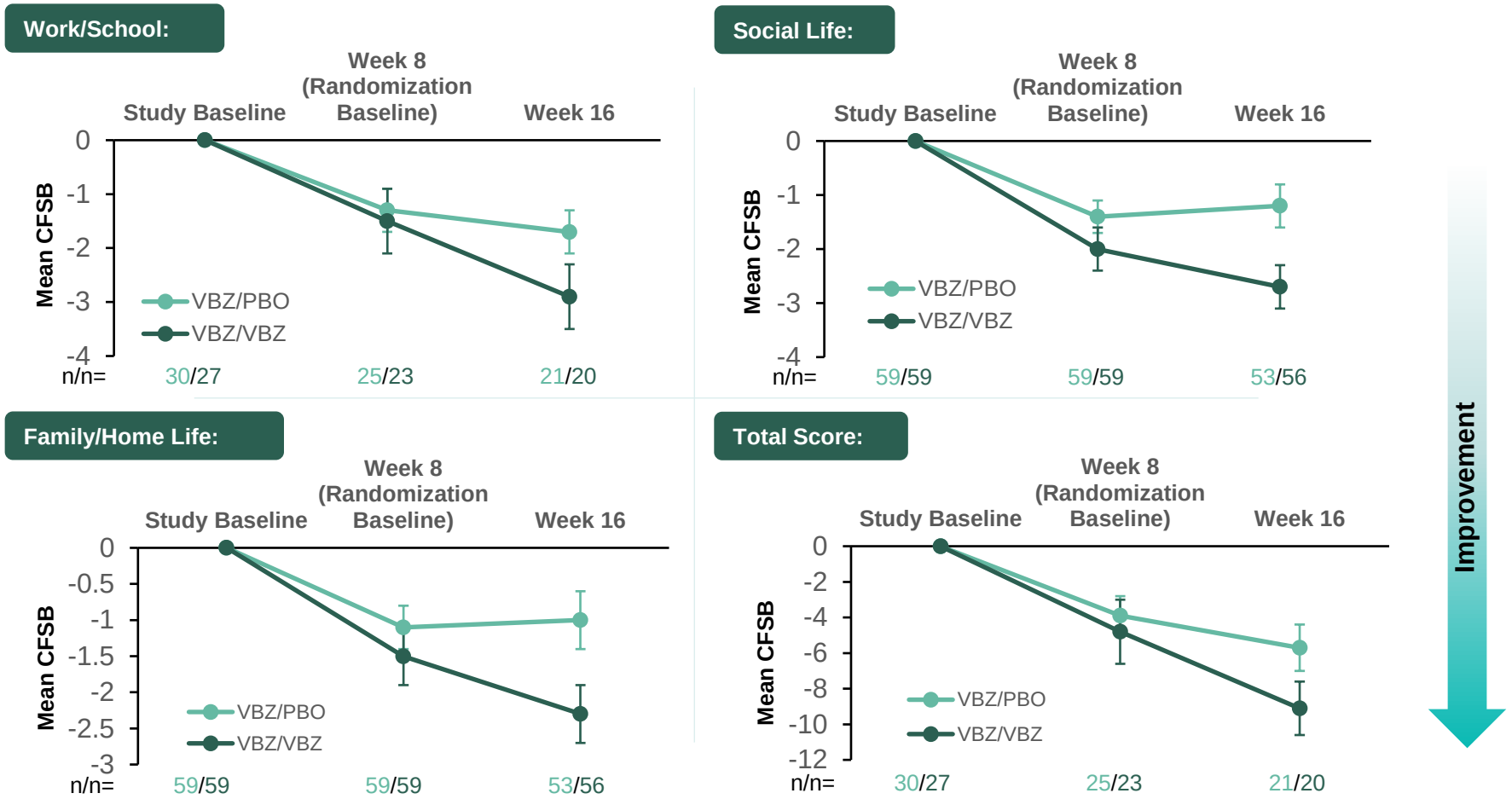
Visual Analog Scale (VAS)	0 to 100	"worst imaginable health state" to "best imaginable health state"

EQ-5D-5L, EuroQoL's 5-Dimension 5-Level questionnaire; PBO, placebo; VAS, visual analog scale; VBZ, valbenazine.

Jimenez R, et al. ISPOR EU 2021.

Study 4002 – Randomized Withdrawal: SDS Score Change from Baseline to Week 16

- Similar to the mean improvements from study baseline to Week 16 for EQ-5D-5L, functional status (SDS) were also greater in patients who continued taking valbenazine



CFSB, change from study baseline.; EQ-5D-5L, EuroQoL's 5-Dimension 5-Level questionnaire PBO, placebo; SDS, Sheehan Disability Scale; VBZ, valbenazine.

Jimenez R, et al. ISPOR EU 2021.

Study 4002 – Randomized Withdrawal: TEAEs

		DBPC Treatment Period	
	OL VBZ Period (N=132)	VBZ/PBO (N=59)	VBZ/VBZ (N=59)
Summary, n (%)			
Any TEAE	43 (32.6)	19 (32.2)	14 (23.7)
Any Serious TEAE	3 (2.3)	2 (3.4)	1 (1.7)
Any TEAE leading to discontinuation	4 (3.0)	1 (1.7)	0 (0)
Deaths[a]	1 (0.8)	0 (0)	0 (0)
TEAEs by preferred term, n (%)[b]			
Pain in extremity	5 (3.8)	0 (0)	0 (0)
Somnolence	4 (3.0)	0 (0)	0 (0)
UTI	4 (3.0)	6 (10.2)	0 (0)
Weight Increased	2 (1.5)	0 (0)	2 (3.4)
Fall	2 (1.5)	2 (3.4)	0 (0)
Anemia	1 (0.8)	2 (3.4)	1 (1.7)
Suicidal Ideation[c]	1 (0.8)	2 (3.4)	1 (1.7)
Blood CPK Increased	1 (0.8)	0 (0)	2 (3.4)
Blood Glucose Increased	0 (0)	0 (0)	2 (3.4)

[a]One subject had a fatal accidental overdose during OL treatment that was judged not related to study drug; this subject was also included in the count for serious TEAEs.

[b]Reported in ≥3% of participants in any treatment group.

[c]All three participants who experienced suicidal ideation during the study had a lifetime history of suicidality

CPK, creatine phosphokinase; DBPC, double-blind, placebo-controlled; OL, open-label; PBO, placebo; TEAE, treatment-emergent adverse event; UTI, urinary tract infection; VBZ, valbenazine.

Jimenez R, et al. ISPOR EU 2021.

Study 4002 – Randomized Withdrawal: Summary

- Valbenazine effects diminished after treatment withdrawal at the Week 8 randomization timepoint; however, compared to study baseline, there is some persistence of effect in the 8 weeks following withdrawal of valbenazine (VBZ/PBO)
- Overall mean improvements in TD movements, health status/quality of life, and functionality at work/school, social life and family life were greater in patients who continued receiving once-daily valbenazine
- During the open-label valbenazine treatment period, 32.6% of all participants had ≥ 1 TEAE
- During the randomized withdrawal, 32.3% of the VBZ/PBO group and 23.7% of the VBZ/VBZ group had ≥ 1 TEAE
  - Urinary tract infection was the only TEAE reported by ≥5% of participants in any treatment group (VBZ/PBO, n=6 [10.2%])
  - There were no clinically important changes in laboratory parameters, vital signs, or ECG parameters

ECG, electrocardiogram; PBO, placebo; TD, tardive dyskinesia; TEAE, treatment-emergent adverse event; VBZ, valbenazine.

Jimenez R, et al. ISPOR EU 2021.

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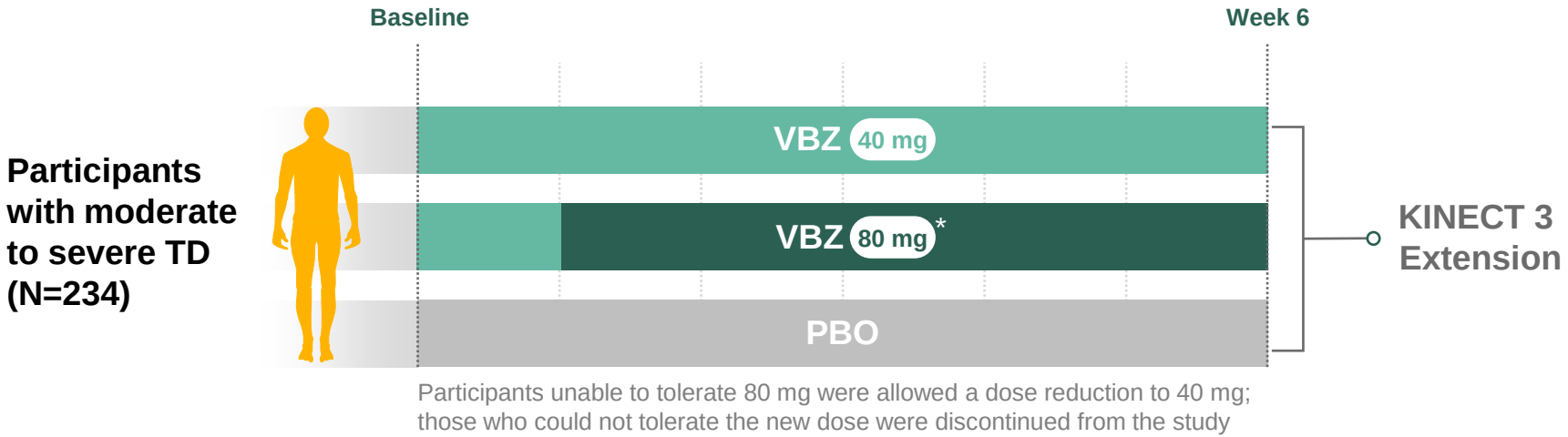
Appendix

KINECT 3 – Early Improvement Analysis: Full 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

*80-mg group received 40 mg for the first week.

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.

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

KINECT 3 – Early Improvement Analysis: Eligibility Criteria[1,2]

Key inclusion criteria

- Diagnosis of schizophrenia, schizoaffective disorder, or mood disorder (DSM-IV)
- Stable psychiatric status (BPRS score <50 at screening)
- DSM diagnosis of neuroleptic-induced TD for ≥3 months prior to screening
- Moderate or severe TD, qualitatively assessed by an external reviewer at screening
- Stable doses of concomitant medications to treat psychiatric and medical disorders were allowed

Key exclusion criteria

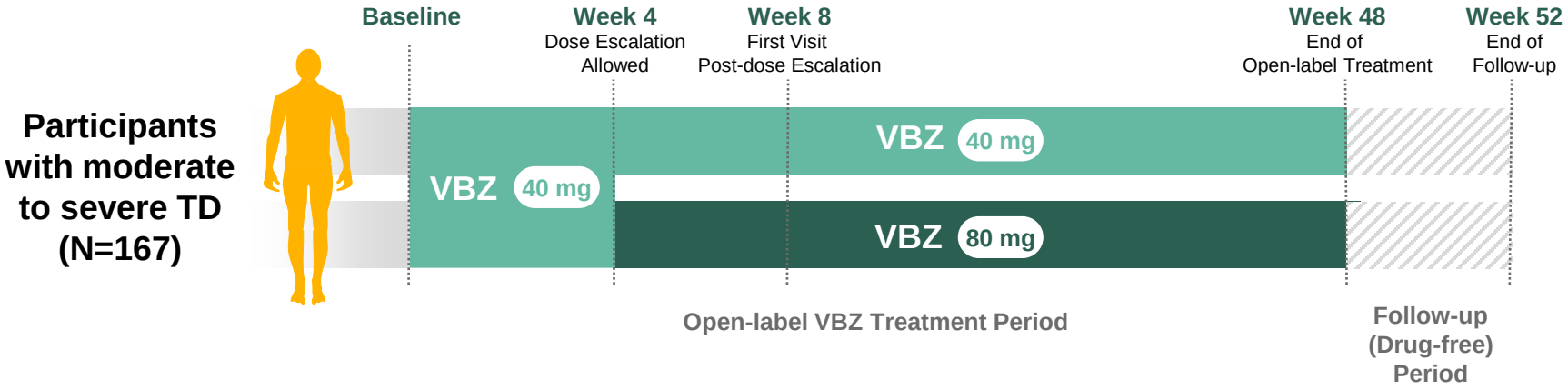
- Active, clinically significant, and unstable medical condition ≤1 month prior to screening
- Comorbid movement disorder more prominent than TD
- Significant risk for active suicidal ideation, suicidal behavior, or violent behavior

BPRS, Brief Psychiatric Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; TD, tardive dyskinesia.

Factor SA, et al. MDS 2019; Nice, France

KINECT 4 Full Study Design

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



Dosing

- All participants received valbenazine 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.
*80-mg group received 40 mg for the first week.

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

KINECT 3 – Early Improvement Analysis: Baseline Characteristics by Global Improvement at Week 2

- Baseline demographics and disease characteristics were generally similar between participants who achieved early PGIC or CGI-TD improvement and those who did not

	PGIC ≤3 "Minimally improved" or better (n=72)	PGIC ≥4 "No change" or worse (n=71)	CGI-TD ≤3 "Minimally improved" or better (n=61)	CGI-TD ≥4 "No change" or worse (n=81)
Demographics				
Age, mean (SD), years	55.8 (9.6)	55.4 (9.3)	55.3 (8.6)	55.8 (10.1)
Male, n (%)	43 (59.7)	34 (47.9)	31 (50.8)	45 (55.6)
White, n (%)	47 (65.3)	34 (47.9)	35 (57.4)	46 (56.8)
BMI, mean (SD), kg/m^2	28.3 (5.9)	28.3 (5.7)	29.2 (5.5)	27.8 (5.9)
Disease characteristics				
Schizophrenia/schizoaffective disorder, n (%)	49 (68.1)	45 (63.4)	39 (63.9)	54 (66.7)
Mood disorder, n (%)	23 (31.9)	26 (36.6)	22 (36.1)	27 (33.3)
C-SSRS lifetime suicidality, n (%)	31 (43.1)	27 (38.0)	24 (39.3)	33 (40.7)
Age at diagnosis, mean (SD)				
Schizophrenia/schizoaffective disorder	29.2 (10.3)	30.2 (14.5)	29.3 (11.0)	29.7 (13.4)
Mood disorder	35.2 (16.8)	31.1 (10.8)	33.9 (15.0)	32.6 (13.6)
Tardive dyskinesia	47.1 (11.5)	47.8 (12.1)	47.0 (10.4)	47.7 (12.8)
BPRS total score at screening, mean (SD)	29.6 (6.4)	29.5 (7.7)	29.2 (6.0)	29.8 (7.8)
AIMS total score at baseline, mean (SD)	10.2 (3.7)	10.0 (4.1)	9.6 (4.0)	10.4 (3.7)

Results are presented for all participants in each subgroup, regardless of dose. PGIC ≤3: "Minimally improved" or better (patient-reported). PGIC ≥4: "No change" or worse (patient-reported). CGI-TD ≤3: "Minimally improved" or better (clinician-reported). CGI-TD ≥4: "No change" or worse (clinician-reported).
AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; C-SSRS, Columbia-Suicide Severity Rating Scale; PGIC, Patient Global Impression of Change; SD, standard deviation.

Factor SA, et al. MDS 2019; Nice, France

KINECT 4 – Patterns of Improvement: Eligibility Criteria[1,2]

Key inclusion criteria

- Adults aged 18 – 85 years
- Diagnosis of schizophrenia, schizoaffective disorder, or mood disorder
- DSM diagnosis of neuroleptic-induced TD for ≥3 months prior to screening
- Stable psychiatric and medical status
- Stable doses of concomitant medications to treat psychiatric and medical disorders were allowed

Key exclusion criteria

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

DSM, Diagnostic and Statistical Manual of Mental Disorders; TD, tardive dyskinesia.

Correll CU, et al. APA 2021.

KINECT 4 – Patterns of Improvement: Baseline Characteristics by Response Categories

- Mean AIMS total scores were higher (worse) among early and delayed responders (P<0.05 across response categories)
- Late and poor responders had relatively fewer participants with ≥1 maximum AIMS item score of 4 (severe) at baseline (P<0.05), which may have left less “room” for improvement

	Early/ Strong/ Sustained (n=17)	Early/ Sustained (n=23)	Early (n=5)	Delayed (n=46)	Late (n=44)	Poor/ None (n=23)	*P*-Value
Age, mean (SD)	57.6 (8.80)	57.9 (8.82)	59.0 (3.08)	58.7 (7.91)	57.4 (10.54)	57.0 (10.89)	0.7638
Sex, n (%)							
Male	6 (35.3)	13 (56.5)	2 (40.0)	27 (58.7)	22 (50.0)	15 (65.2)	0.4602
Female	11 (64.7)	10 (43.5)	3 (60.0)	19 (41.3)	22 (50.0)	8 (34.8)	
Race, n (%)							
White/Caucasian	11 (64.7)	12 (52.2)	4 (80.0)	35 (76.1)	29 (65.9)	16 (69.6)	0.4767
Black/African-American	5 (29.4)	10 (43.5)	1 (20.0)	11 (23.9)	13 (29.5)	7 (30.4)	
Other[a]	1 (5.9)	1 (4.3)	0 (0)	0 (0)	2 (4.5)	0 (0)	
BMI, mean (SD), kg/m²	28.4 (5.65)	28.7 (5.09)	32.4 (4.55)	27.3 (4.94)	29.4 (5.97)	28.8 (5.61)	0.7614
Psychiatric diagnosis, n (%)							
Schizophrenia/ schizoaffective disorder	12 (70.6)	15 (65.2)	5 (100.0)	35 (76.1)	31 (70.5)	16 (69.6)	0.7583
Mood disorder	5 (29.4)	8 (34.8)	0 (0)	11 (23.9)	13 (29.5)	7 (30.4)	
AIMS total score, mean (SD)	15.8 (4.59)	15.5 (4.88)	14.2 (5.40)	15.8 (4.16)	13.5 (4.78)	13.6 (5.47)	0.0371
Highest AIMS item score, n (%)[b]							
1 = Minimal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.0412
2 = Mild	1 (5.9)	2 (8.7)	0 (0)	0 (0)	0 (0)	0 (0)	
3 = Moderate	7 (41.2)	10 (43.5)	3 (60.0)	24 (52.2)	32 (72.7)	15 (65.2)	
4 = Severe	9 (52.9)	11 (47.8)	2 (40.0)	22 (47.8)	12 (27.3)	6 (26.1)	

[a]Includes Asian, Native Hawaiian/Pacific Islander, and other; [b]In any (1 or more) of the 7 body regions.
AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; SD, standard deviation.
Correll CU, et al. APA 2021.

KINECT 4 – Patterns of Improvement: Baseline Characteristics by Response Categories

- No significant differences in baseline characteristics were found between remitters and non-remitters

	Remission (n=97)	No Remission (n=61)	P-value
Age, mean (SD)	58.6 (9.32)	56.7 (8.94)	0.2100
Sex, n (%)			
Male	46 (47.4)	39 (63.9)	0.0500
Female	51 (52.6)	22 (36.1)	
Race, n (%)			
White/Caucasian	66 (68.0)	41 (67.2)	0.2998
Black/African-American	29 (29.9)	18 (29.5)	
Other[a]	2 (2.1)	2 (3.3)	
BMI, mean (SD), kg/m^2	28.6 (5.58)	28.7 (5.28)	0.8922
Psychiatric diagnosis, n (%)			
Schizophrenia/ schizoaffective disorder	67 (69.1)	47 (77.0)	0.3622
Mood disorder	30 (30.9)	14 (23.0)	
AIMS total score, mean (SD)	14.2 (4.52)	15.6 (5.09)	0.0822
Highest AIMS item score, n (%)[b]			
1 = Minimal	0 (0)	0 (0)	0.2418
2 = Mild	3 (3.1)	2 (3.3)	
3 = Moderate	61 (62.9)	30 (49.2)	
4 = Severe	33 (34.0)	29 (47.5)	

[a]Includes Asian, Native Hawaiian/Pacific Islander, and other; [b]In any (1 or more) of the 7 body regions.
AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; SD, standard deviation.
Correll CU, et al. APA 2021.

Study 4002 – Randomized Withdrawal: Key Eligibility Criteria

Key inclusion criteria

- Adults aged 18 to 85 years
- Clinical diagnosis of schizophrenia, schizoaffective disorder or mood disorder, and neuroleptic-induced TD
- Moderate of severe TD (qualitatively assessed by external reviewer at screening)
- Stable psychiatric and medical status
- Stable doses of concomitant medication to treat psychiatric and medical conditions were allowed

Key exclusion criteria

- Comorbid movement disorder that was more prominent than TD
- Significant risk for active suicidal ideation or suicidal behavior (C-SSRS) or violent behavior

C-SSRS, Columbia-Suicide Severity Rating Scale; TD, tardive dyskinesia.

Jimenez R, et al. ISPOR EU 2021.

Study 4002 – Randomized Withdrawal: Baseline Characteristics by Treatment Group

	VBZ/PBO (n=58)	VBZ/VBZ (n=59)
Age, mean (SD) years	59.2 (8.3)	58.0 (8.0)
Male, (n%)	31 (53.4)	29 (49.2)
Ethnicity, n (%)		
Hispanic or Latino	32 (55.2)	32 (54.2)
Not Hispanic or Latino	26 (44.8)	27 (45.8)
Race, n (%)		
White/Caucasian	36 (62.1)	43 (72.9)
Black/African-American	21 (36.2)	16 (27.1)
Multiple	1 (1.7)	0 (0)
BMI, mean (SD), kg/m^2	28.4 (5.2)	29.3 (4.8)
Psychiatric diagnosis, n (%)		
Schizophrenia/schizoaffective disorder	36 (62.1)	33 (55.9)
Mood disorder (e.g. MDD, bipolar disorder)	22 (37.9)	26 (44.1)
AIMS total score, mean (SD)	10.3 (3.7)	11.0 (4.1)
BPRS score, mean (SD)[a]	28.2 (6.9)	29.0 (7.2)
C-SSRS lifetime suicidal ideation or behavior, n (%)[a]	23 (39.0)	29 (49.2)

[a]BPRS score and C-SSRS lifetime suicidality are shown for the randomized safety analysis set (VBZ/PBO, n=59; VBZ/VBZ, n=59).

AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; MDD, major depressive disorder; PBO, placebo; SD, standard deviation; VBZ, valbenazine.

Jimenez R, et al. ISPOR EU 2021.