Effect of Valbenazine on Tardive Dyskinesia in Participants with Mood Disorders

Neurocrine BIOSCIENCES

MED-MSL-TD-US-0104

McIntyre RS, et al. Journal of Affective Disorders. 2019;246:217-223.

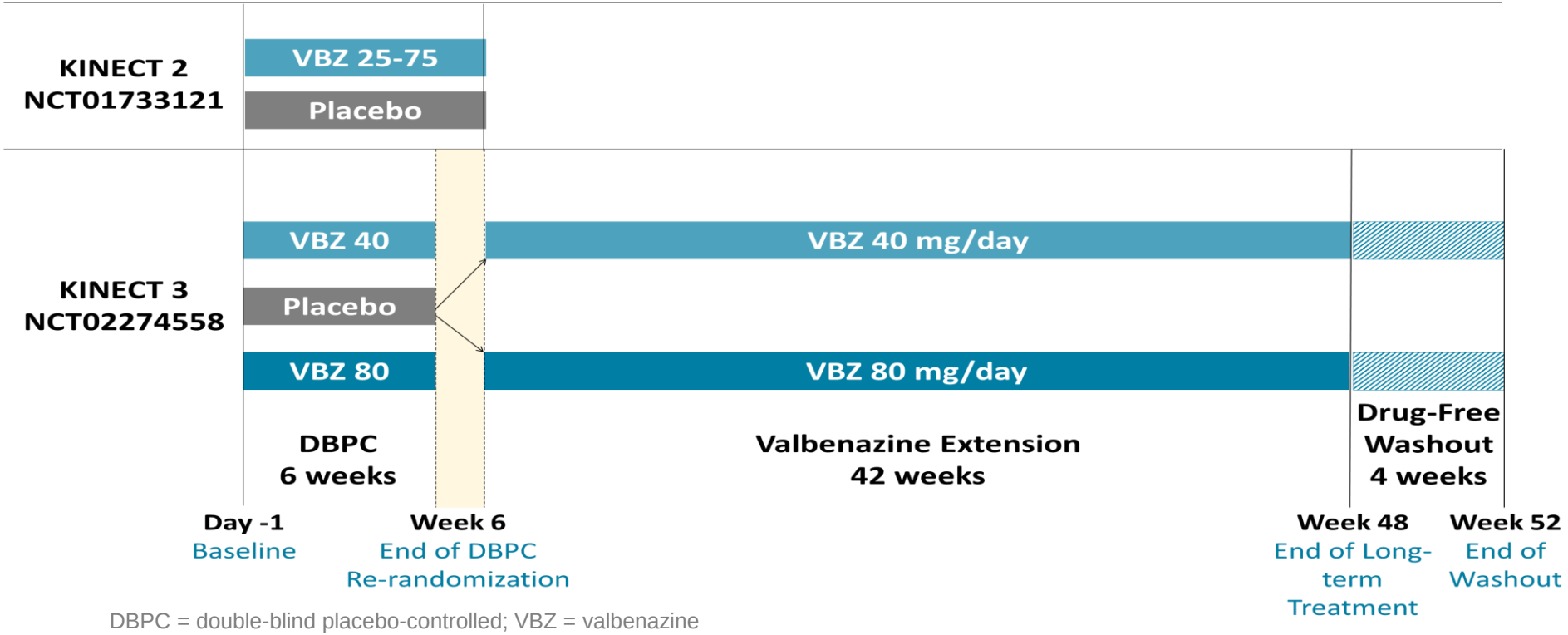
Background

- Many patients with non-psychotic mood disorders, including bipolar disorder and major depressive disorder (MDD) are[1]
  - Highly functional
  - May have higher levels of awareness and distress from relatively less noticeable abnormal movements
- Although SGAs were initially anticipated to be less likely to cause TD than FGAs, evidence indicates the risk for developing TD is an important clinical consideration for both SGAs and FGAs[2]
  - Expanding use of SGAs in other diagnoses than psychotic disorders contributes to rising number of patients with TD
- Pooled data from KINECT 2 and KINECT 3 studies were analyzed post hoc to further characterize the mood disorder subgroups and evaluate their response to treatment with valbenazine[3]
  - These studies were not designed or powered for statistical testing within the mood diagnosis subgroup

SGAs, Second generation antipsychotics; FGAs, First generation antipsychotics.

1. Daniel, SJ, et al. 2016. Int. J. Sci. Study 4, 17–20.
2. Cloud, LJ, et al. 2014. Neurotherapeutics 11, 166–176.
3. McIntyre RS, et al. Journal of Affective Disorders. 2019;246:217-223.

Clinical Study Design



DBPC = double-blind placebo-controlled; VBZ = valbenazine

- Post Hoc pooled analysis evaluating the effects of once-daily valbenazine on TD in adults with a mood disorder

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Baseline Characteristics

Characteristics	Placebo (n = 44)	Valbenazine 40 mg (n = 28)	Valbenazine 80 mg (n = 42)
Age, mean (SD), years	56.8 (11.7)	54.9 (8.5)	56.1 (10.6)
Male, *n* (%)	14 (31.8)	12 (42.9)	19 (45.2)
Race, *n* (%)			
White	36 (81.8)	21 (75.0)	27 (64.3)
Black	7 (15.9)	6 (21.4)	13 (31.0)
Other	1 (2.3)	1 (3.6)	2 (4.8)
Body mass index, mean (SD), kg/m^2	28.4 (4.9)	29.3 (5.6)	28.6 (5.8)
Mood disorder diagnosis, *n* (%)[a,b]			
Bipolar disorder	23 (52.3)	16 (57.1)	30 (71.4)
With history of substance abuse	6 (13.6)	3 (10.7)	10 (23.8)
Depression / major depression	21 (47.7)	11 (39.3)	11 (26.2)
With history of substance abuse	2 (4.5)	1 (3.6)	1 (2.4)
Other / unspecified mood disorder	0	1 (3.6)	1 (2.4)

[a] Diagnoses based on verbatim investigator terms as follows: bipolar disorder (bipolar disorder, bipolar 1, bipolar I disorder, bipolar, bipolar mixed, bipolar affective disorder, bipolar mood disorder, bipolar depressed, bipolar depressed with psychotic features, mood disorder bipolar type); depression/major depression (MDD, MDD with psychosis, MDD recurrent, major depression, severe depression, atypical depression, depression and anxiety); [b] Substance abuse based on the following MedDRA preferred terms: alcohol abuse, alcoholism, drug abuse, drug abuser, drug dependence, polysubstance dependence, substance abuse.
AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation; YMRS, Young Mania Rating Scale;

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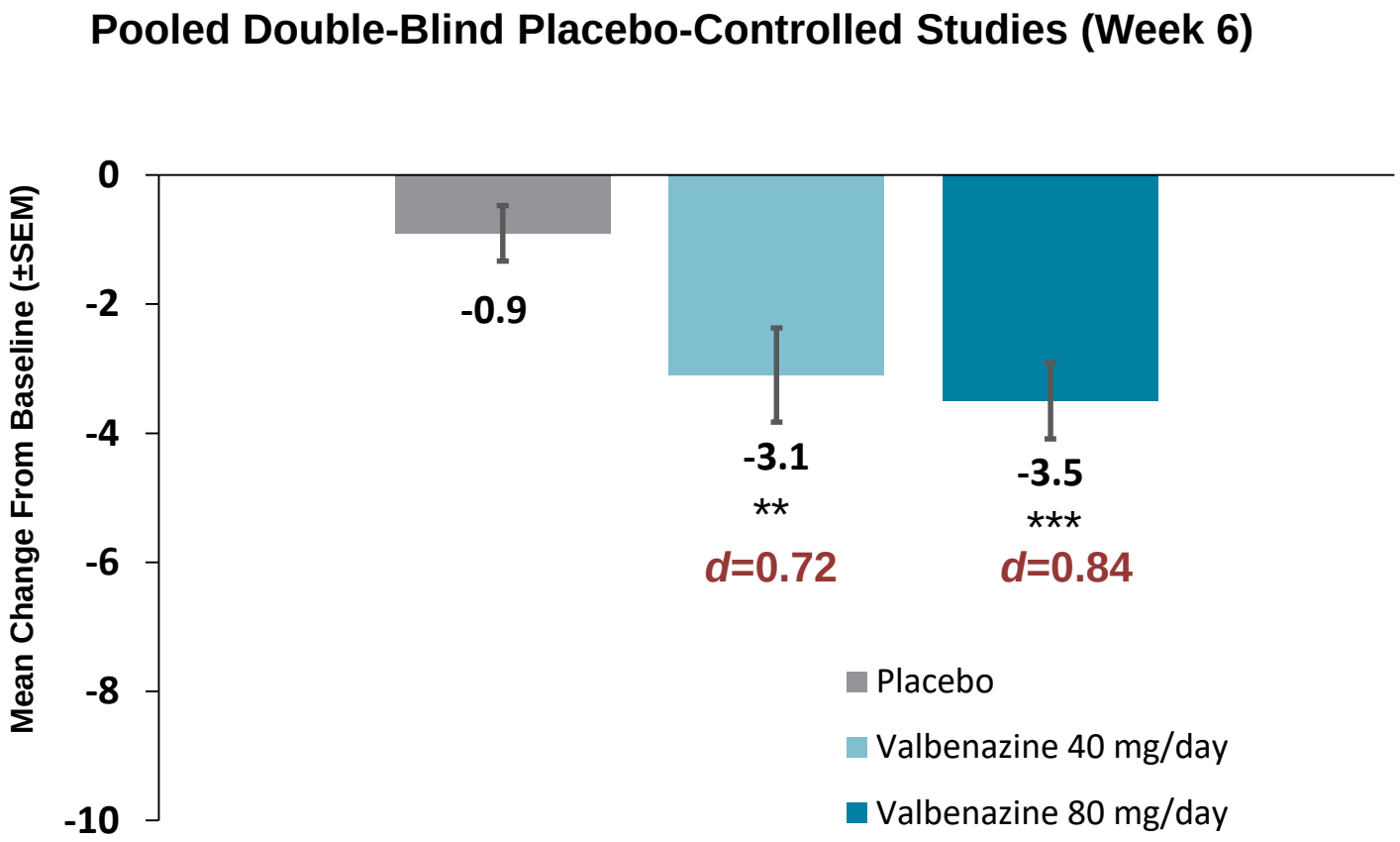
Baseline Characteristics (Continued)

Characteristics	Placebo (n = 44)	Valbenazine 40 mg (n = 28)	Valbenazine 80 mg (n = 42)
Age at diagnosis, mean (SD), years			
Mood disorder	34.7 (13.8)	33.7 (16.5)	37.8 (13.2)
Tardive dyskinesia	51.9 (13.1)	49.5 (8.7)	50.3 (11.1)
Suicidal ideation or behavior, *n* (%)[a]			
Lifetime history	14 (31.8)	13 (46.4)	22 (52.4)
Recent history (prior 3 months)	1 (2.3)	4 (14.3)	2 (4.8)
Antipsychotic use at baseline, n (%)	27 (61.4)	22 (78.6)	22 (52.4)
Atypical only	24 (54.5)	19 (67.9)	21 (50.0)
Typical only or typical + atypical	3 (6.8)	3 (10.7)	1 (2.4)
Baseline scores, mean (SD)			
BPRS total	25.5 (6.1)	27.0 (5.4)	27.1 (6.4)
YMRS total	1.8 (2.3)	2.9 (2.9)	3.5 (3.2)
MADRS total	5.3 (3.5)	7.6 (3.8)	6.0 (4.0)
AIMS total	10.2 (4.6)	11.4 (3.6)	10.0 (3.7)

[a] Based on endorsement of Columbia-Suicide Severity Rating Scale items 1-10

AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation; YMRS, Young Mania Rating Scale;

AIMS Total Score Mean Changes from Baseline to Week 6



**$P < 0.01$; ***$P < 0.001$ versus placebo. Based on least squares mean differences between valbenazine and placebo: 40 mg/day, -2.2; 80 mg/day, -2.6; AIMS, Abnormal Involuntary Movement Scale; *d*, Cohen's effect size; SEM standard error of the mean.

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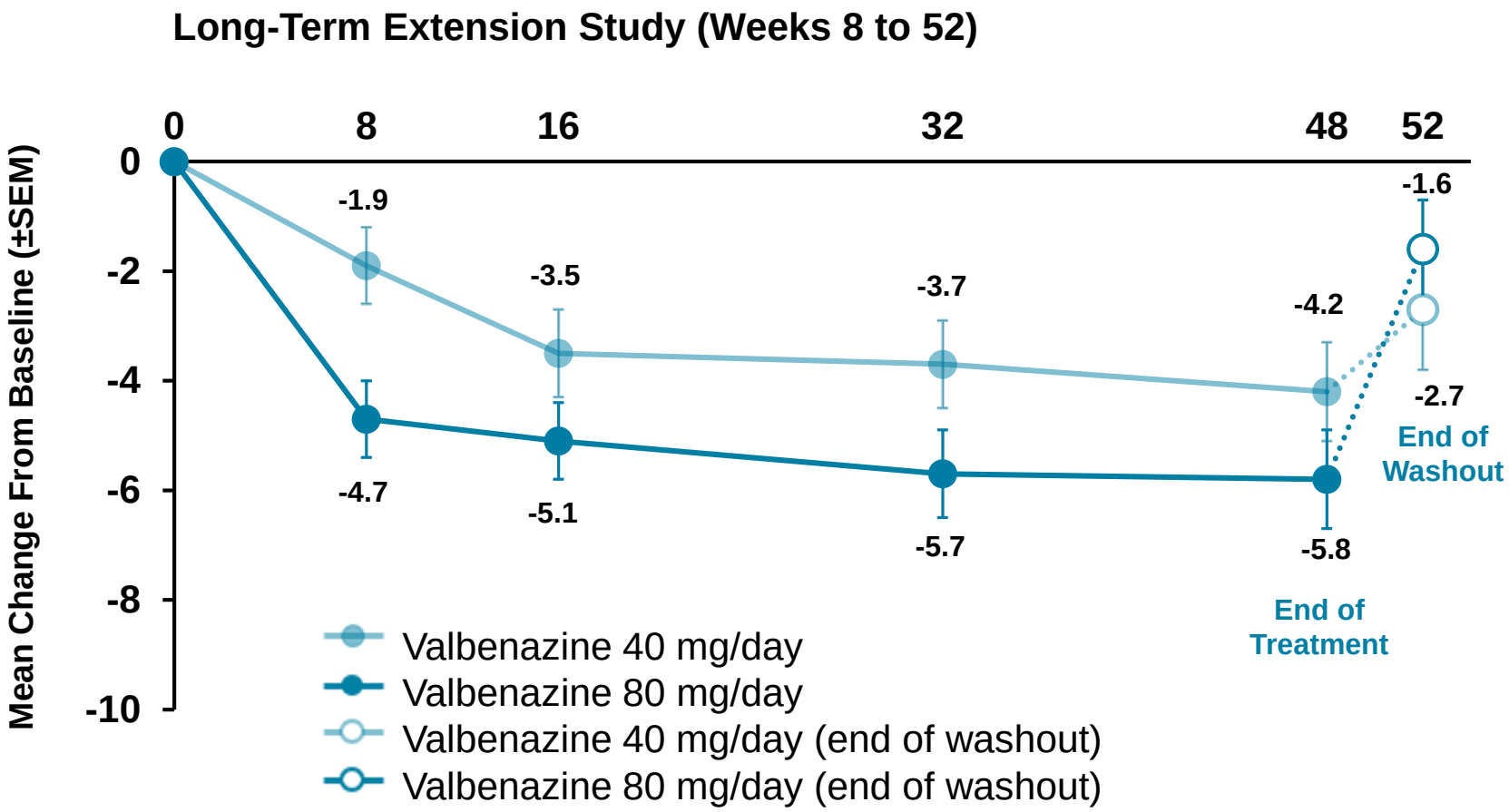
AIMS Total Score Mean Change from Baseline



AIMS, Abnormal Involuntary Movement Scale; SEM standard error of the mean.
*Subjects in the initial placebo group were re-randomized to valbenazine (VBZ) 40 mg or VBZ 80 mg after Week 6. Subjects re-randomized to VBZ 80 mg received VBZ 40 mg for the first week.

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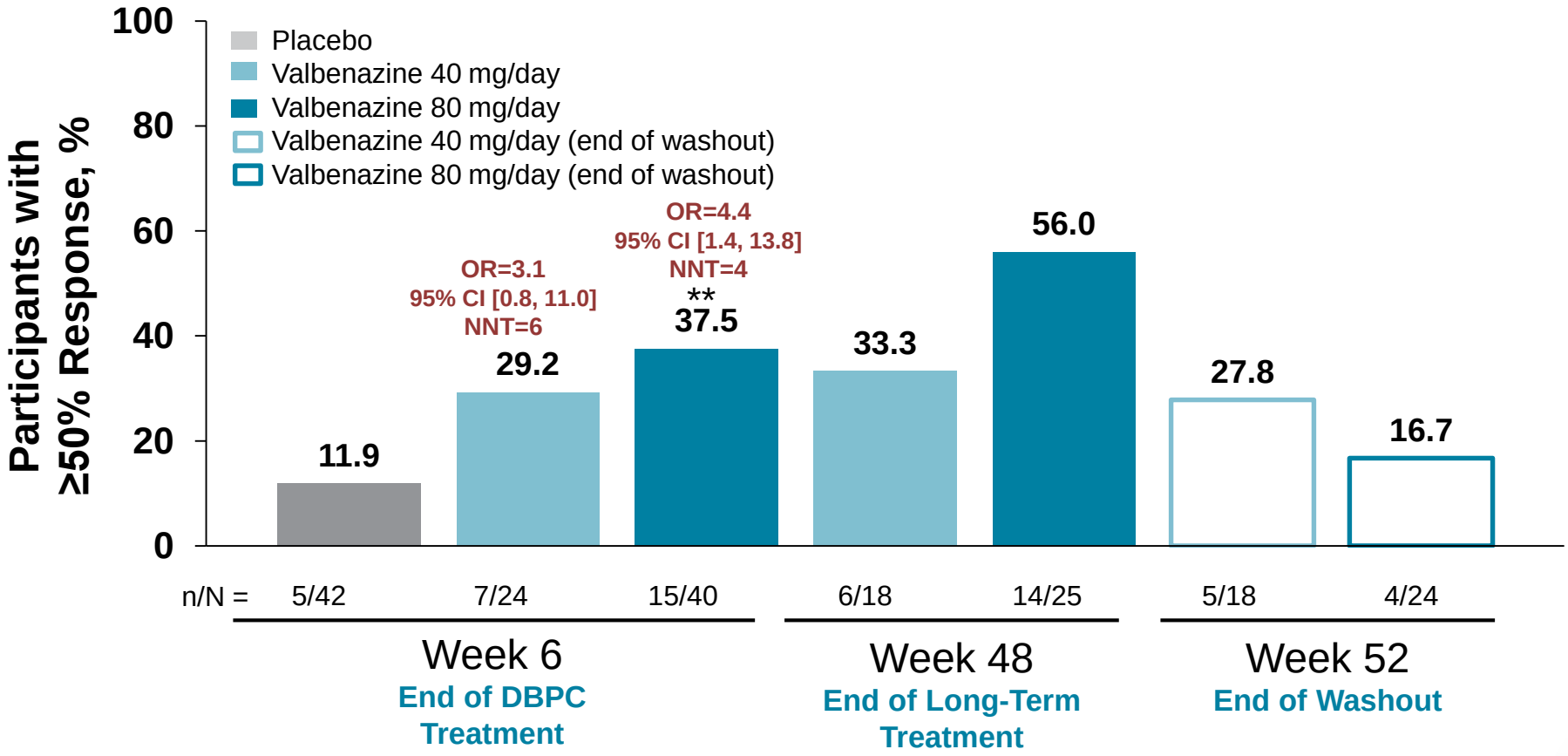
≥50% Total AIMS Score Improvement from Baseline



***P* < 0.01 versus placebo; AIMS, Abnormal Involuntary Scale; CI, confidence interval; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; DBPC, double-blind placebo-controlled; NNT, number needed to treat; OR, odds ratio; PGIC, Patient Global Impression of Change.

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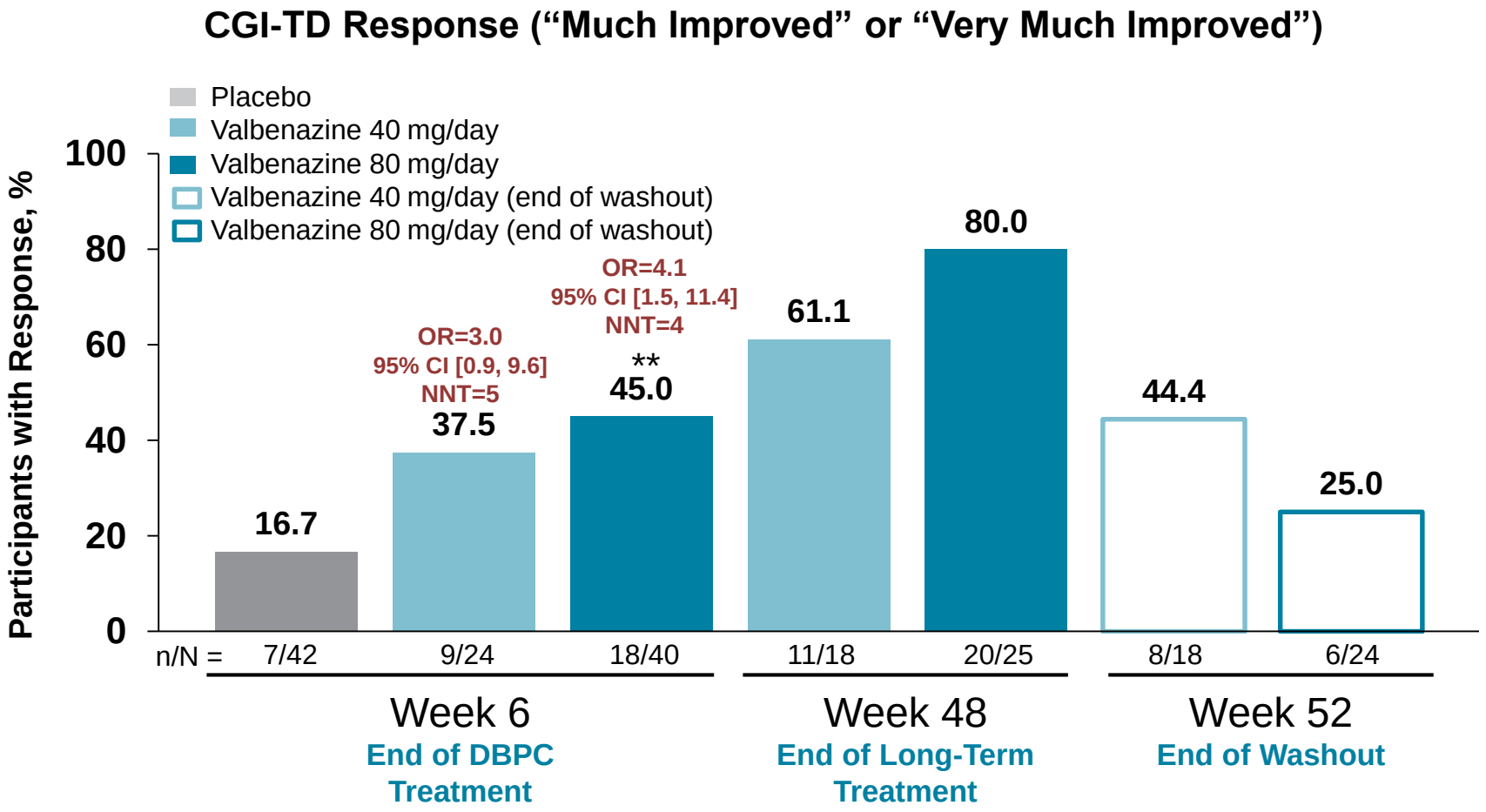
CGI-TD Response



***P* < 0.01 versus placebo.

AIMS, Abnormal Involuntary Scale; CI, confidence interval; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; DBPC, double-blind placebo-controlled; NNT, number needed to treat; OR, odds ratio; PGIC, Patient Global Impression of Change.

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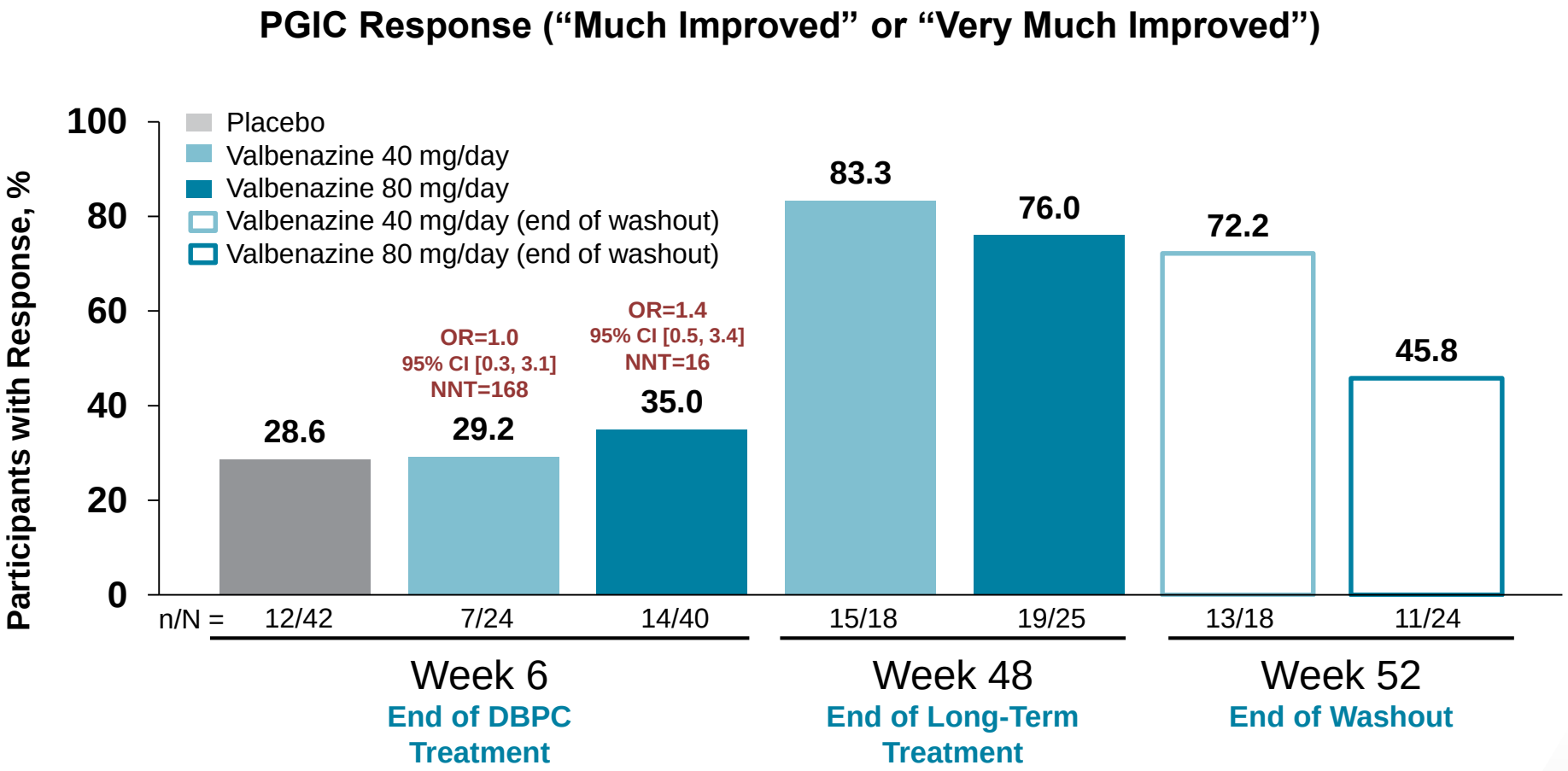
PGIC Response



AIMS, Abnormal Involuntary Scale; CI, confidence interval; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; DBPC, double-blind placebo-controlled; NNT, number needed to treat; OR, odds ratio; PGIC, Patient Global Impression of Change.

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Safety

Treatment-Emergent Adverse Events(TEAE), n(%)	Placebo (n = 44)	Valbenazine 40 mg (n = 28)	Valbenazine 80 mg (n = 42)
Any TEAE	17 (38.6)	14 (50.0)	23 (54.8)
Serious TEAE	0	1 (3.6)	0
TEAE leading to discontinuation	0	2 (7.1)	0
TEAEs by preferred term[a]			
Headache	2 (4.5)	2 (7.1)	4 (9.5)
Vomiting	0	1 (3.6)	4 (9.5)
Dyskinesia	0	0	3 (7.1)
Fatigue	0	3 (10.7)	2 (4.8)
Nausea	1 (2.3)	2 (7.1)	2 (4.8)
Akathisia	0	2 (7.1)	2 (4.8)
Somnolence	1 (2.3)	7 (25.0)	1 (2.4)
Dry mouth	0	3 (10.7)	0
Constipation	4 (9.1)	2 (7.1)	0

[a] Reported in ≥5% of participants in either valbenazine treatment group.
TEAE, treatment-emergent adverse event;

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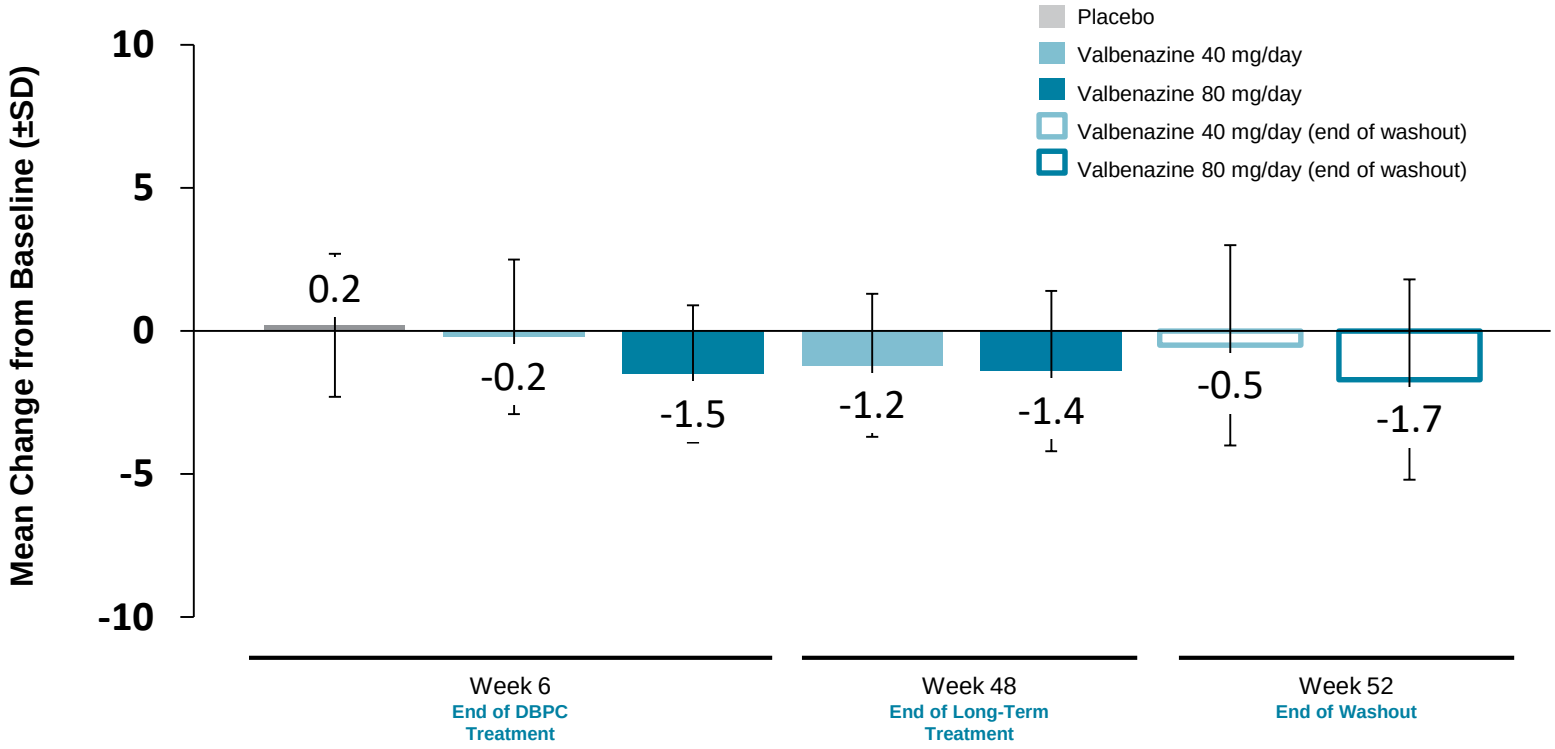
Young Mania Rating Scale (Total Score)



In participants who received ≥1 dose of study drug and had an available assessment at the study visit; DBPC, double-blind placebo-controlled; SD, standard deviation; YMRS, Young Mania Rating Scale.

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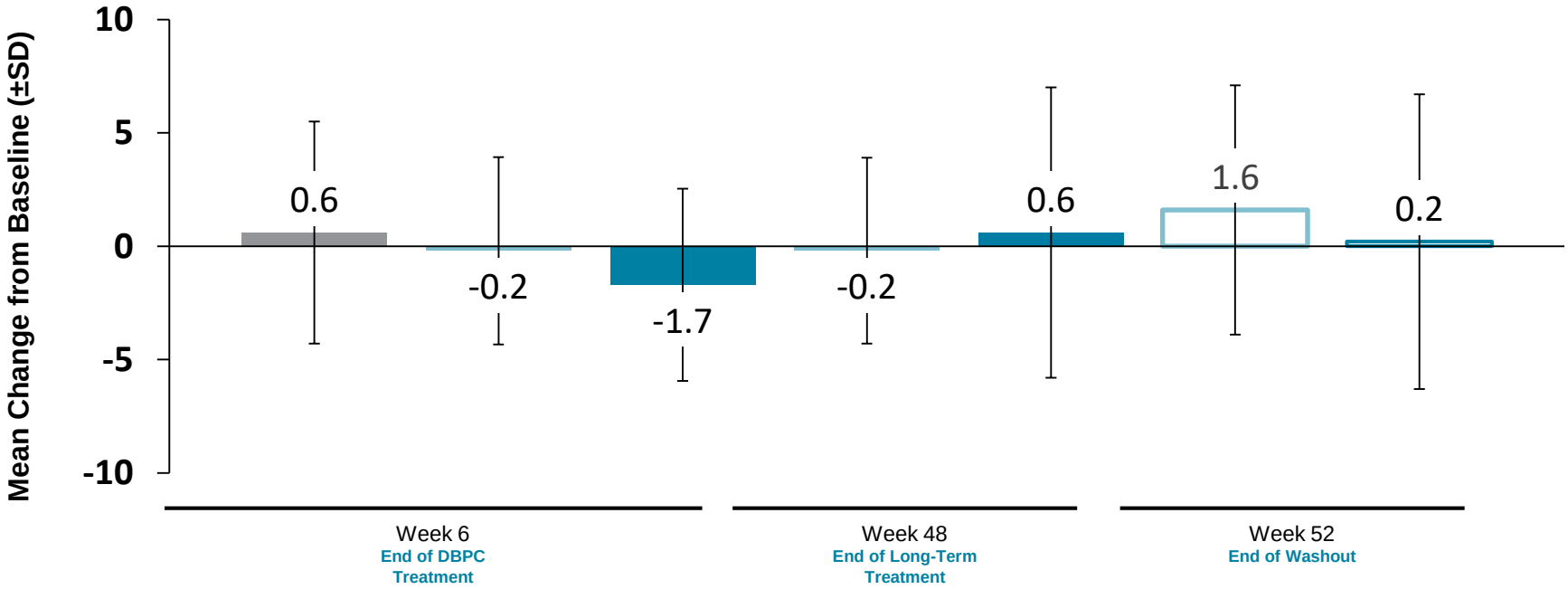
Montgomery-Åsberg Depression Rating Scale (Total Score)



In participants who received ≥1 dose of study drug and had an available assessment at the study visit; DBPC, double-blind placebo-controlled; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation

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Summary

- KINECT 2 and KINECT 3 studies showed clinically meaningful TD improvements in participants with mood disorders, including bipolar disorder and MDD
- Valbenazine was generally well tolerated, with no new TEAEs
  - Mean changes from baseline in movement scale scores (BARS, SAS), vital signs, ECG parameters, and key laboratory parameters were minimal
- Psychiatric rating scales (YMRS & MADRS) generally remained stable

Barnes Akathisia Rating Scale, BARS; Simpson-Angus Scale, SAS; Montgomery-Åsberg Depression Rating Scale, MADRS; Young Mania Rating Scale, YMRS.

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Back-up

Sample Size

- Pooled double-blind population
  - 114 participants from KINECT 2 & KINECT 3
    - Placebo (n=44)
    - Pooled 40 mg/day group (n=28) included participants who received
      - 50 mg/day (KINECT 2)
      - 40 mg/day (KINECT 3)
    - Pooled 80 mg/day group (n=42) included participant who received
      - 75 mg/ day (KINECT 2)
      - 80 mg/day (KINECT 3)
- Long-term population (n=77) included participants from the KINECT 3 extension study
  - 40 mg/day group (n=36)
  - 80 mg/day group (n=41)

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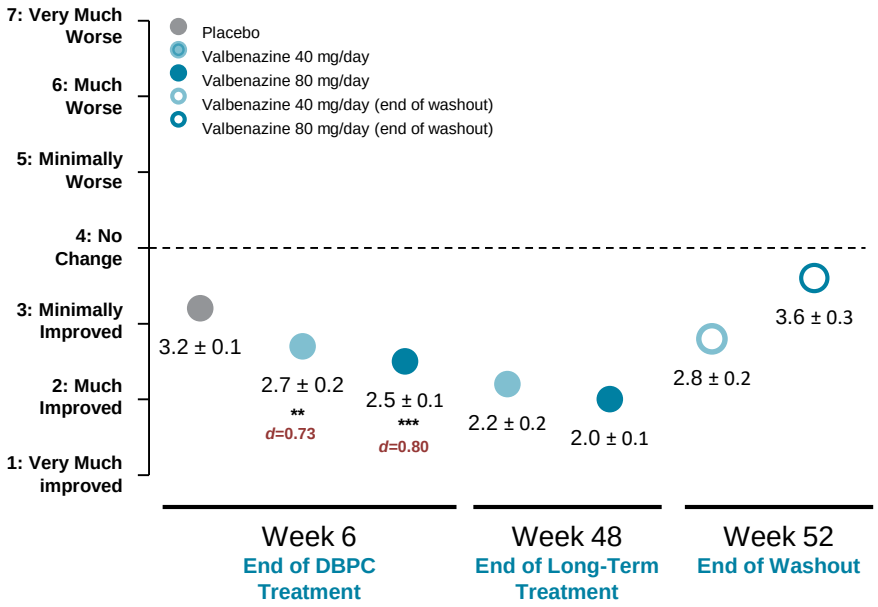
Analyses

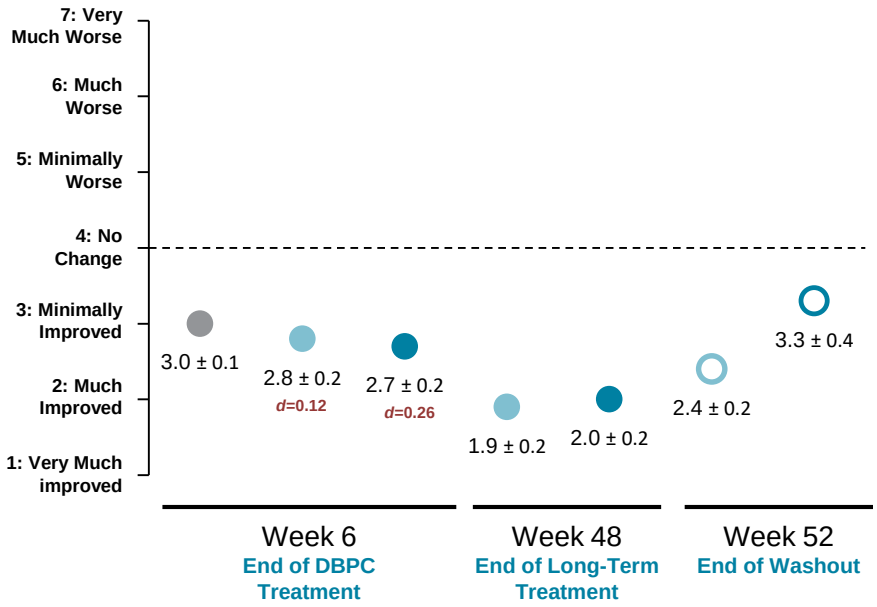
- Efficacy Assessments
  - Primary Endpoint: Abnormal Involuntary Movement Scale (AIMS)
  - Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD)
  - Patient Global Impression of Change (PGIC)
- Safety Assessments
  - Treatment-emergent adverse events (TEAEs)
  - Clinical laboratory tests, vital sign measurements, & ECGs
  - Emergence of suicidal ideation or behavior - Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Psychiatric status - Young Mania Rating Scale (YMRS) & Montgomery–Åsberg Depression Rating Scale (MADRS)
  - Treatment-emergent akathisia and parkinsonism - Barnes Akathisia Rating Scale (BARS) & Simpson Angus Scale (SAS)

CGI-TD and PGIC Mean Scores

CGI-TD



PGIC



Mean scores (± standard error of the mean) are presented. ***P* < 0.01; ****P* < 0.001 versus placebo. Based on least squares mean differences between valbenazine and placebo for CGI-TD (40 mg/day, -0.6; 80 mg/day, -0.7) and PGIC (40 mg/day, -0.1; 80 mg/day, -0.3).
CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; *d*, Cohen's effect size; DBPC, double-blind placebo-controlled; PGIC, Patient Global Impression of Change.