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KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup

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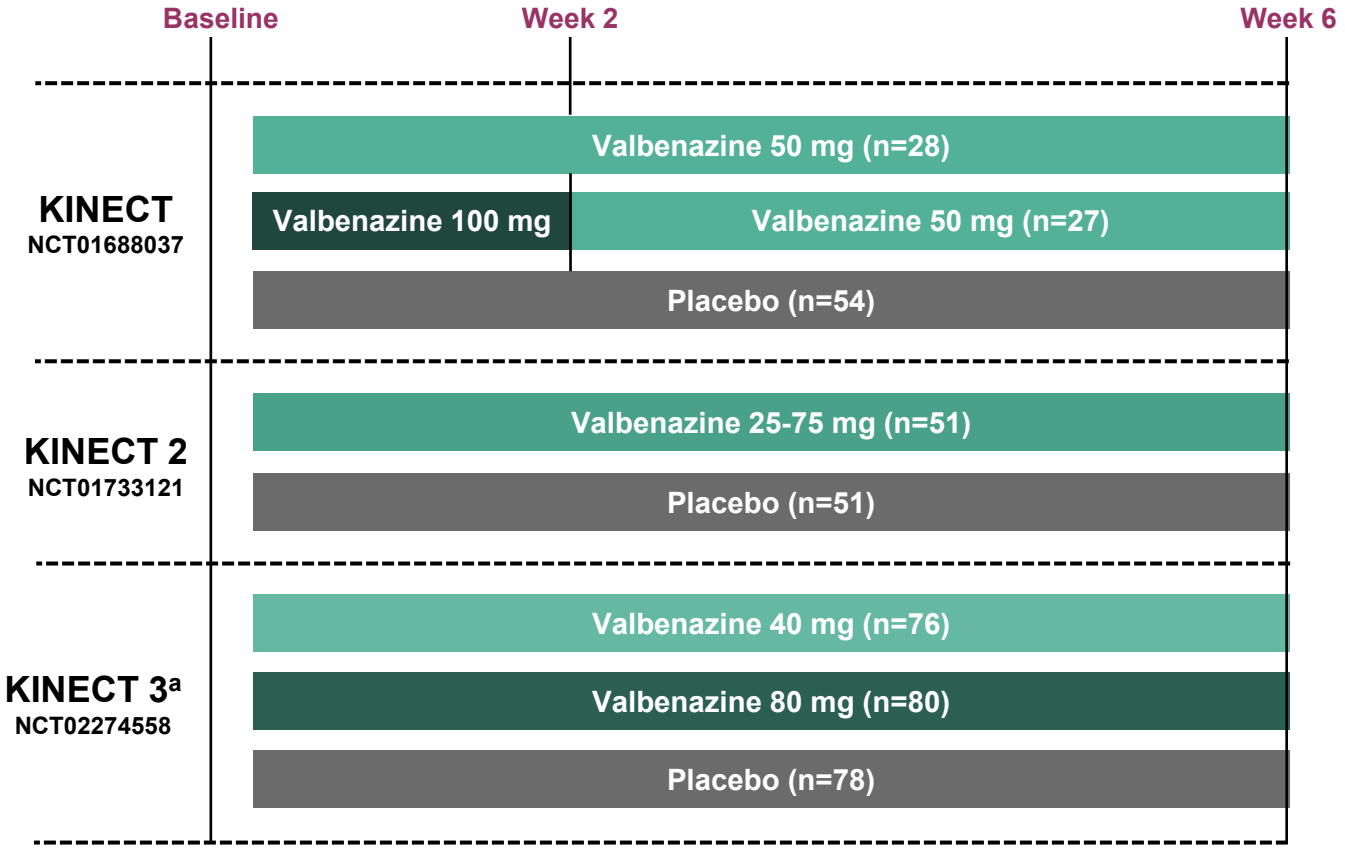
KINECT, KINECT 2, & KINECT 3: Study Design



- Pooled valbenazine 80 mg group included participants from KINECT 3 (80 mg group) and KINECT 2 (75 mg group)
- Pooled valbenazine 40 mg group included participants from in KINECT 3 (40 mg group) and KINECT (50 mg group)
- Participants who received only valbenazine 25 mg in KINECT 2 study were excluded from analyses

[a]KINECT 100 mg group received 100 mg for the first two weeks then decrease to 50 mg. [b]KINECT 3 80 mg group received 40 mg for the first week.
N-values indicate the number of participants who were randomized to treatment.

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KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: Key Inclusion/Exclusion Criteria

- Key inclusion criteria:
  - *Diagnostic and Statistical Manual of Mental Disorders* (e.g., DSM-IV) diagnosis of schizophrenia, schizoaffective disorder, or mood disorder; required to be psychiatrically stable prior to study entry[a]
    - KINECT 2 also included participants with a gastrointestinal disorder (e.g., gastroparesis, GERD)
  - DSM diagnosis of DRBA-induced TD for ≥3 months prior to screening
  - Moderate or severe TD as qualitatively assessed by blinded external AIMS reviewers
    - KINECT study included participants with moderate or severe TD in AIMS Item 8 (severity of abnormal movement overall) as assessed by blinded external AIMS reviewers
- Key exclusion criteria:
  - Active, clinically significant, and unstable medical condition within 1 month prior to screening
  - Comorbid movement disorder that was more prominent than TD
  - Significant risk for active suicidal ideation, suicidal behavior, or violent behavior
- Concomitant medications to treat psychiatric disorders were allowed and stable doses were encouraged throughout the studies

[a] e.g., Brief Psychiatric Rating Scale score <50 at screening

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KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: Assessments & Methods

- Measures used to evaluate changes in TD severity in all subgroups included:
  - Mean change from baseline to Week 6 in the Abnormal Involuntary Movement Scale (AIMS) total score
  - AIMS threshold response (defined as a ≥50% total score improvement from baseline to Week 6)
  - Clinical relevance for AIMS mean score change was evaluated using Cohen's *d* effect size
  - Clinical relevance for AIMS response was evaluated using number needed to treat (NNT) and odds ratios (ORs) with 95% confidence intervals (95% CIs)
    - Valbenazine (VBZ) dose groups were combined for OR analyses
- Population subgroups were defined as:
  - Psychiatric diagnosis: schizophrenia/schizoaffective disorder, mood disorder
  - Antipsychotic medication use at baseline: yes, no
  - Anticholinergic medication use at baseline: yes, no
  - Lifetime history of suicidality: yes, no
  - Age: 18 to <55 years, ≥55 years
  - Sex: male, female
  - TD duration: <7 years, ≥7 years
  - CYP2D6 genotype: poor metabolizer (PM), non-PM
  - Body mass index (BMI), kg/m2: 18.5 to <25, 25 to <30, ≥30
- These data are based on post-hoc analyses

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KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: AIMS Mean Score at Baseline

Subgroups	Placebo (N=158)		Valbenazine 40 mg (N=114)		Valbenazine 80 mg (N=101)	
	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)
Psychiatric diagnosis						
Schizophrenia/schizoaffective disorder	116 (73.4)	8.4 (4.3)	90 (78.9)	8.4 (4.2)	61 (60.4)	9.1 (3.6)
Mood disorder	42 (26.6)	10.2 (4.6)	24 (21.1)	11.3 (3.6)	40 (39.6)	10.2 (3.6)
Antipsychotic use						
Yes	130 (82.3)	8.6 (4.1)	102 (89.5)	8.7 (4.1)	77 (76.2)	9.0 (3.4)
No	28 (17.7)	9.9 (5.7)	12 (10.5)	11.4 (4.2)	24 (23.8)	11.3 (3.9)
Anticholinergic use						
Yes	48 (30.4)	8.3 (4.2)	44 (38.6)	9.0 (4.3)	34 (33.7)	9.6 (4.1)
No	110 (69.6)	9.1 (4.5)	70 (61.4)	9.1 (4.2)	67 (66.3)	9.5 (3.4)
Lifetime suicidality[a]						
Yes	60 (38.0)	8.6 (3.6)	48 (42.1)	8.9 (4.0)	41 (40.6)	10.2 (3.3)
No	98 (62.0)	9.0 (4.9)	66 (57.9)	9.1 (4.4)	60 (59.4)	9.1 (3.8)

- The largest subgroups (>250 total participants) were:
  - CYP2D6 non-PM (n=354)
  - Concomitant antipsychotic use (n=309)
  - TD duration ≥7 years (n=306)
  - Schizophrenia/schizoaffective disorder (n=267)

[a]Suicidal behavior and/or ideation, based on the Columbia-Suicide Severity Rating Scale.

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KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: AIMS Mean Score at Baseline

Subgroups	Placebo (N=158)		Valbenazine 40 mg (N=114)		Valbenazine 80 mg (N=101)	
	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)
Age						
18 to <55 years	65 (41.1)	9.0 (3.9)	51 (44.7)	8.1 (4.2)	38 (37.6)	9.4 (4.0)
≥55 years	93 (58.9)	8.8 (4.8)	63 (55.3)	9.8 (4.1)	63 (62.4)	9.6 (3.4)
Sex						
Male	89 (56.3)	8.6 (4.0)	72 (63.2)	8.6 (3.9)	55 (54.5)	9.3 (3.6)
Female	69 (43.7)	9.2 (4.9)	42 (36.8)	9.7 (4.7)	46 (45.5)	9.8 (3.7)
Tardive dyskinesia duration						
<7 years	11 (7.0)	5.7 (2.2)	11 (9.6)	9.1 (3.6)	10 (9.9)	9.2 (3.7)
≥7 years	133 (84.2)	9.3 (4.4)	94 (82.5)	8.8 (4.3)	79 (78.2)	9.4 (3.7)
CYP2D6 genotype[b]						
Poor metabolizer	6 (3.8)	8.5 (3.9)	7 (6.1)	9.9 (3.1)	4 (4.0)	12.8 (1.7)
Non-poor metabolizer	152 (96.2)	8.9 (4.5)	106 (93.0)	8.9 (4.2)	96 (95.0)	9.4 (3.7)
Body mass index						
18.5 to <25 kg/m^2	42 (26.6)	9.2 (5.6)	28 (24.6)	9.1 (4.2)	30 (29.7)	10.4 (3.5)
25 to <30 kg/m^2	51 (32.3)	9.2 (4.3)	38 (33.3)	10.3 (4.5)	26 (25.7)	9.7 (4.1)

[b]Participants are counted only once by CYP2D6 genotype.
AIMS, Abnormal Involuntary Movement Scale; SD, standard deviation.

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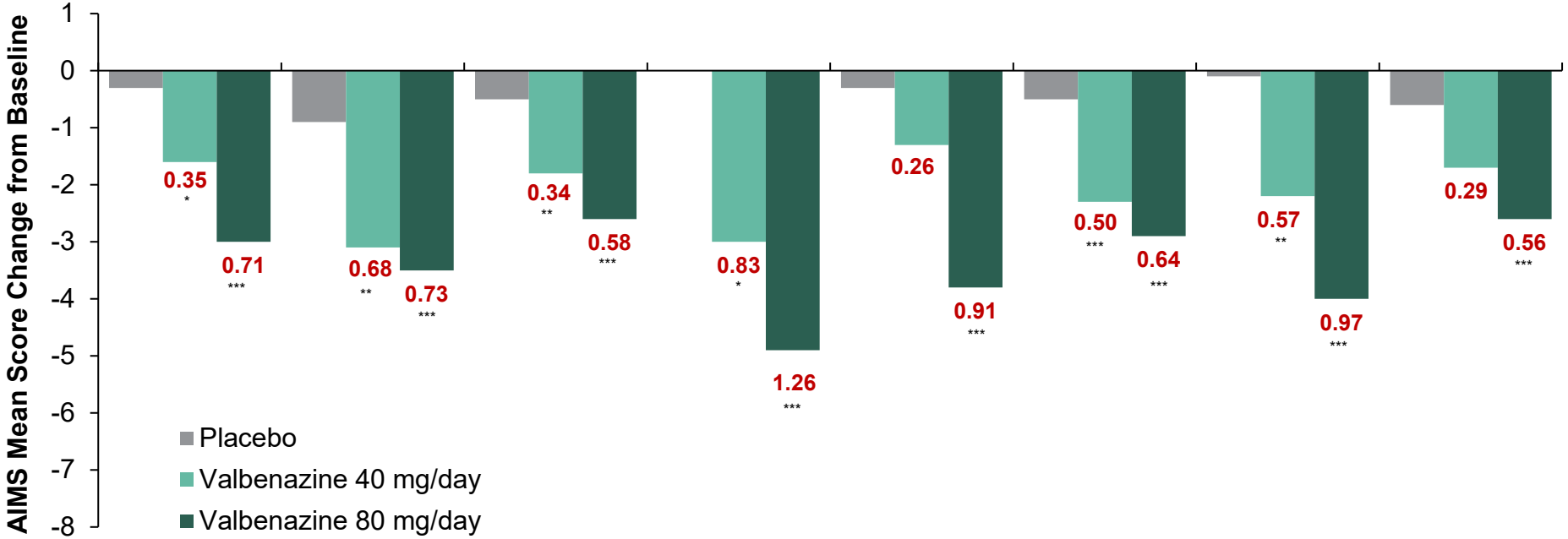
KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: AIMS Total Score Mean Changes from Baseline to Week 6

	Psychiatric Diagnosis		Antipsychotic Use		Anticholinergic Use		Lifetime Suicidality	
	Schizophrenia[a]	Mood disorder	Yes	No	Yes	No	Yes	No
Placebo, n	116	42	130	28	48	110	60	98
VBZ 40 mg, n	90	24	102	12	44	70	48	66
VBZ 80 mg, n	61	40	77	24	34	67	41	60



[a]Includes schizophrenia or schizoaffective disorder.
*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ vs placebo. Cohen's *d* effect sizes are indicated in red.
VBZ, valbenazine.

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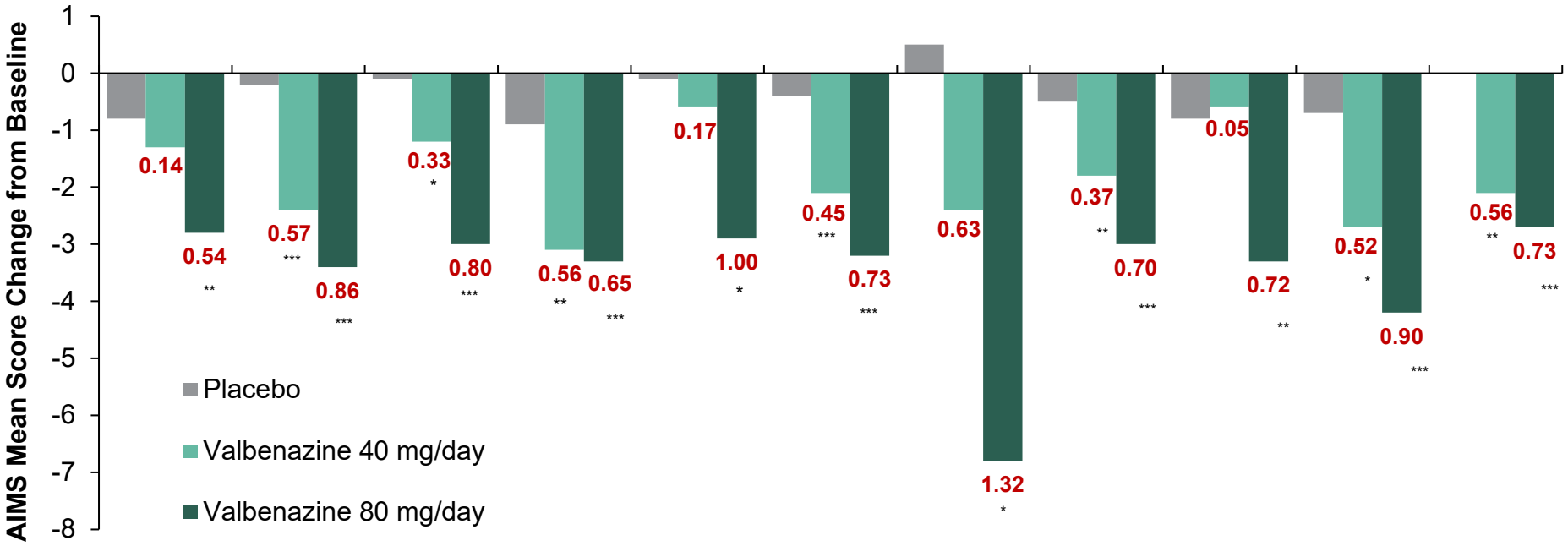
KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: AIMS Total Score Mean Changes from Baseline to Week 6

	Age		Sex		TD Duration		CYP2D6 Genotype		Body Mass Index kg/m²		
	18 to <55 yr	≥55 yr	Male	Female	<7 yr	≥7 yr	PM	Non-PM	18.5 to <25	25 to <30	≥30
Placebo, n	65	93	89	69	11	133	6	152	42	51	63
VBZ 40 mg, n	51	63	72	42	11	94	7	106	28	38	47
VBZ 80 mg, n	38	63	55	46	10	79	4	96	30	26	40



*P≤0.05, **P≤0.01, ***P≤0.001 vs placebo. Cohen's *d* effect sizes are indicated in red.
PM, poor metabolizer; TD, tardive dyskinesia; VBZ, valbenazine.

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KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: Total Score Mean Changes from Baseline to Week 6

- In all subgroups mean changes in AIMS total score from baseline to Week 6 indicated greater improvements with valbenazine relative to placebo
  - A significant difference between valbenazine 80 mg and placebo ($P<0.05$) was found in all subgroups
  - Subgroups with the largest effect sizes ($d \geq 0.8$) for valbenazine 80 mg were:
    - Age ≥55 years
    - Men
    - TD duration <7 years
    - No concomitant antipsychotic use (also 40 mg)
    - Concomitant anticholinergic use
    - History of lifetime suicidality
    - CYP2D6 PM genotype
    - BMI 25 to <30 kg/m2

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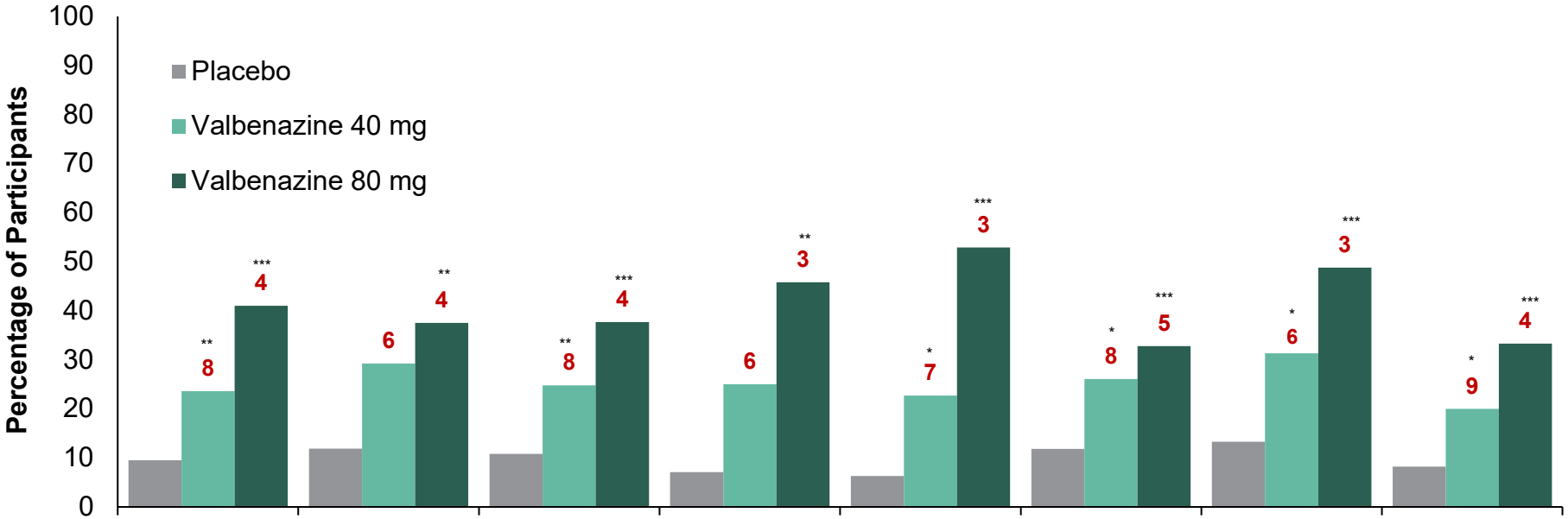
KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: Response (≥50% Total Score Improvement) at Week 6



	Psychiatric Diagnosis		Antipsychotic Use		Anticholinergic Use		Lifetime Suicidality	
	Schizophrenia[a]	Mood disorder	Yes	No	Yes	No	Yes	No
Placebo, n	116	42	130	28	48	110	60	98
VBZ 40 mg, n	90	24	102	12	44	70	48	66
VBZ 80 mg, n	61	40	77	24	34	67	41	60

[a]Includes schizophrenia or schizoaffective disorder.
*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$ vs placebo. Numbers needed to treat are indicated in red; VBZ, valbenazine.

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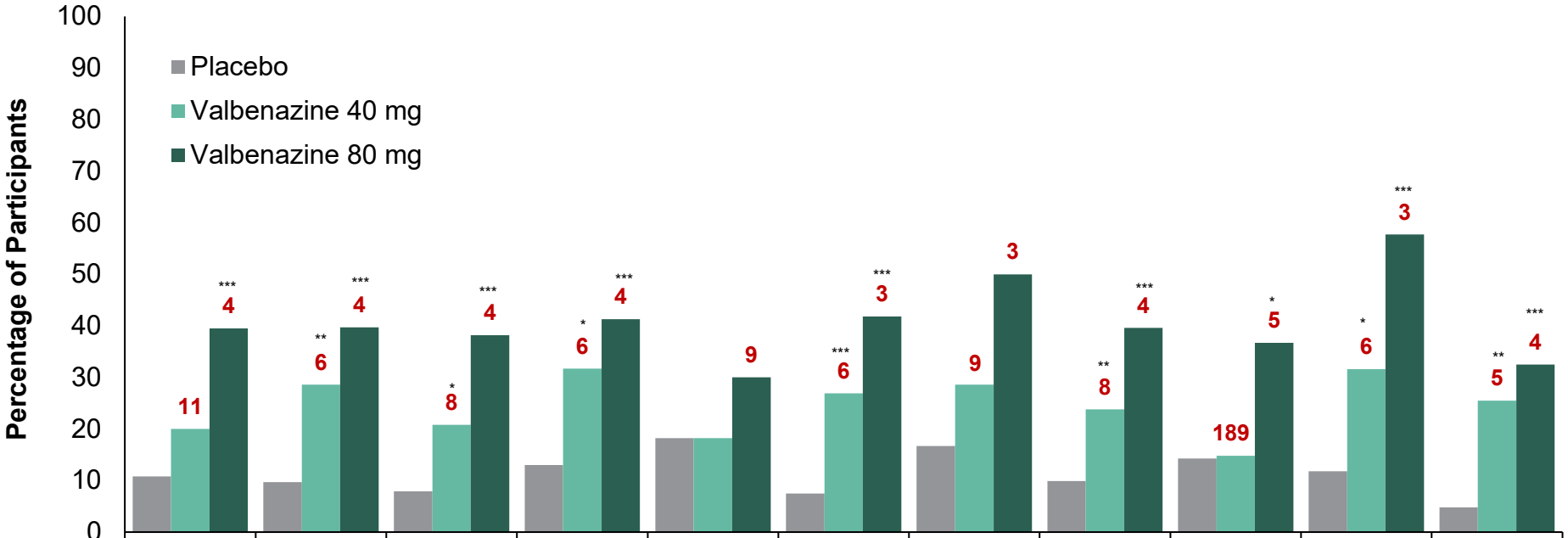
KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: Response (≥50% Total Score Improvement) at Week 6



Placebo, n	65	93	89	69	11	133	6	152	42	51	63
VBZ 40 mg, n	51	63	72	42	11	94	7	106	28	38	47
VBZ 80 mg, n	38	63	55	46	10	79	4	96	30	26	40

*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$ vs placebo. Numbers needed to treat are indicated in red. A negative value indicates a lower AIMS response (≥50% total score improvement from baseline) with valbenazine vs placebo. In one subgroup (TD duration <7 years), the NNT for 40 mg could not be calculated because the difference from placebo was 0%.
PM, poor metabolizer; TD, tardive dyskinesia; VBZ, valbenazine.

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KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: Response (≥50% Total Score Improvement) at Week 6

- The percentage of participants with an AIMS ≥50% response was generally higher with valbenazine relative to placebo
  - A significant difference between valbenazine 80 mg and placebo ($P<0.05$) was found in all subgroups except for participants with TD duration <7 years and CYP2D6 PM
  - All subgroups treated with valbenazine 80 mg had a NNT ≤5, except for participants with TD duration <7 years (NNT=9)

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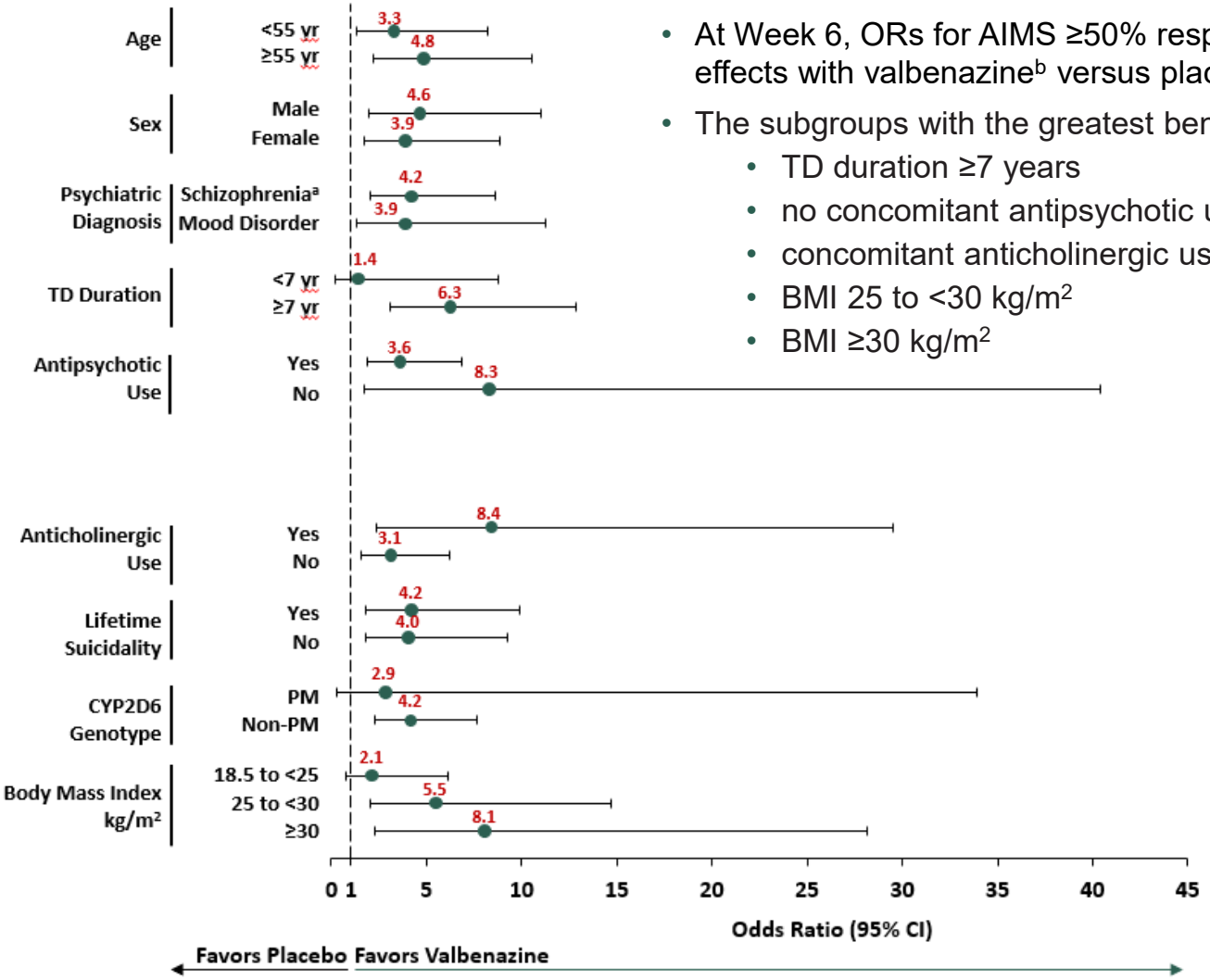
KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: Odds Ratios for AIMS Response at Week 6 (Pooled ITT Population)



- At Week 6, ORs for AIMS ≥50% response indicated favorable effects with valbenazine[b] versus placebo in all subgroups
- The subgroups with the greatest benefit (OR >5.0) were:
  - TD duration ≥7 years
  - no concomitant antipsychotic use
  - concomitant anticholinergic use
  - BMI 25 to <30 kg/m^2
  - BMI ≥30 kg/m^2

[a]Includes schizophrenia or schizoaffective disorder. Odds ratios are indicated in red. CI, confidence interval; PM, poor metabolizer; TD, tardive dyskinesia
[b]40 and 80 mg combined

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KINECT, KINECT 2, & KINECT 3 – AIMS Analysis by Subgroup: Summary

- In all subgroups, mean changes in AIMS total score from baseline to Week 6 indicated greater improvements with valbenazine (VBZ) relative to placebo
  - A significant difference between valbenazine 80 mg and placebo ($P<0.05$) was found in all subgroups
- The percentage of participants with an AIMS ≥50% response was generally higher with VBZ relative to placebo
  - A significant difference between VBZ 80 mg and placebo ($P<0.05$) was found in all subgroups except for participants with TD duration <7 years and CYP2D6 PM ($P>0.05$)
- At Week 6, odds ratios (ORs) for AIMS ≥50% response indicated favorable effects with valbenazine versus placebo in all subgroups
  - The subgroups with the greatest benefit (OR >5.0) were TD duration ≥7 years (6.3), no concomitant antipsychotic use (8.3), concomitant anticholinergic use (8.4), BMI 25 to <30 kg/m^2 (5.5), and BMI ≥30 kg/m^2 (8.1)

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