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RESEARCH ARTICLE

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The effects of valbenazine on tardive dyskinesia in older and younger patients

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Objective: To evaluate the effects of once-daily valbenazine (40 or 80 mg/d) in older and younger adults with tardive dyskinesia (TD).

Methods: Data were pooled from three 6-week, randomized, double-blind, placebo-controlled (DBPC) studies (KINECT [NCT01688037], KINECT 2 [NCT01733121], and KINECT 3 [NCT02274558]) and two long-term studies (KINECT 3 extension and KINECT 4 [NCT02405091]). Outcomes analyzed in older and younger participants (55 years or older and younger than 55 years, respectively) included Abnormal Involuntary Movement Scale (AIMS) response (threshold of greater than or equal to 50% improvement from baseline in total score [items 1 to 7]) and Clinical Global Impression of Change—Tardive Dyskinesia (CGI-TD) response (score 2 or less ["very much improved" or "much improved"]). Safety assessments included treatment-emergent adverse events (TEAEs).

Results: At week 6 (end of DBPC treatment), the percentage of participants who met the AIMS response threshold was higher with valbenazine versus placebo in both subgroups: 55 years or older (80 mg/d, 39.7% [$P < .001$]; 40 mg/d, 28.6% [$P < .01$]; placebo, 9.7%); younger than 55 years (80 mg/d, 39.5% [$P < .001$]; 40 mg/d, 20.0% [$P > .05$]; placebo, 10.8%). The percentage of participants with CGI-TD response was also higher with valbenazine versus placebo: 55 years or older (80 mg/d, 41.3% [$P < .01$]; 40 mg/d, 30.2% [$P > .05$]; placebo, 19.4%); younger than 55 years (80 mg/d, 39.5% [$P < .05$]; 40 mg/d, 35.3% [$P < .05$]; placebo, 18.5%). Responses at week 48 (end of long-term treatment, combined doses) were as follows: 55 years or older (AIMS, 70.7%; CGI-TD, 82.8%); younger than 55 years (AIMS, 58.7%; CGI-TD, 72.3%). No significant differences between older and younger subgroups were found for AIMS or CGI-TD response. No new safety signals or TEAEs of clinical concern were found in older participants who received long-term treatment.

Conclusions: Valbenazine improved TD and was generally well tolerated in older and younger adults.

KEYWORDS

age, clinical trial, efficacy, older adults, safety, tardive dyskinesia, tolerability, valbenazine

1 | INTRODUCTION

As the US population ages, the prevalence of serious mental illnesses (SMIs) is rising. Since SMIs can reduce life expectancy by 10 to 20 years,[1,2] standard cutoffs used to define "elderly" in healthy populations (ie, 60 or 65 years) may not be applicable to patients with an SMI. Moreover, treatment of SMIs with an antipsychotic may result in tardive dyskinesia (TD), an often persistent movement disorder characterized by involuntary movements in the face, trunk, and/or extremities.[3-5]

Older patients are at higher risk for TD than younger patients, even when they are treated with lower doses or a shorter duration.[6-8] In studies of first-generation antipsychotics, the estimated cumulative incidence of TD in older patients was approximately 25% after 1 year of exposure and 55% to 60% after 3 years of exposure.[8,9] TD is associated with greater psychiatric symptom severity, lower likelihood of improved psychopathology, more severe motor side effects, cognitive difficulties, and decreased quality of life.[10-13] TD can also cause balance and respiratory problems that may be particularly worrisome in the older population,[14,15] as well as depression or feelings of embarrassment that contribute to social isolation.[14,16] Given the wide use of antipsychotic agents in older patients for psychiatric and behavioral reasons,[17] more research is needed to determine best practices for treating TD in older patients.

Valbenazine is a novel vesicular monoamine transporter 2 (VMAT2) inhibitor approved for treating TD in adults, with no required dose adjustments for age.[18] In pharmacokinetic studies of healthy volunteers, valbenazine was rapidly absorbed and slowly eliminated, allowing for once-daily dosing; no observed differences in mean plasma concentrations, peak serum concentrations, or overall exposure were found between older and younger participants.[19,20] The effects of valbenazine on TD were evaluated in several double-blind, placebo-controlled (DBPC) trials (KINECT [NCT01688037], KINECT 2 [NCT01733121], and KINECT 3 [NCT02274558]),[21-23] a blinded extension study (KINECT 3),[24] and a long-term open-label study (KINECT 4 [NCT02405091]).[25] Data from these studies were analyzed post hoc to evaluate TD response, psychiatric symptoms and suicidality, and safety/tolerability in older (age 55 years or older) and younger (aged younger than 55 years) individuals with antipsychotic-related TD.

Key points

- Compared with younger adults, older patients treated with an antipsychotic have a greater risk for tardive dyskinesia, a persistent and potentially irreversible movement disorder that may contribute to poorer health, problems with balance and mobility, decreased quality of life, feelings of depression or embarrassment, and increased social isolation.
- In the double-blind, placebo-controlled, clinical studies, older participants (55 years or older, n = 249) had significantly greater improvements in tardive dyskinesia with once-daily valbenazine versus placebo over 6 weeks, with results that were comparable with younger participants (younger than 55 years, n = 178).
- Long-term studies (up to 48 weeks) indicated that older participants (n = 190) continued to demonstrate improvements in tardive dyskinesia, with generally good tolerability, no new safety concerns, and no apparent emergence of drug-induced parkinsonism.

2 | METHODS

2.1 | Study designs, pooling, and age subgroups

Three DBPC studies and two long-term studies were included for analyses (Figure S1). Methods and results of the individual studies are published[21-25]; eligibility criteria are summarized in the Supporting Information. Study protocols were approved by institutional review boards, and all patients provided written informed consent.

Valbenazine treatment in the DBPC studies was as follows: KINECT (50 or 100 mg/d for 2 weeks, 50 mg/d for 4 weeks); KINECT 2 (25 to 75 mg/d for 6 weeks, escalated in 25-mg/d increments every 2 weeks on the basis of response and tolerability); KINECT 3 (40 or 80 mg/d for 6 weeks). Valbenazine treatment in the long-term studies was as follows: KINECT 3 extension (40 or 80 mg/d [blinded dose] for 42 weeks, 4-week washout); KINECT 4 (40 or 80 mg/d [open label], 4-week washout). Participants unable to tolerate valbenazine 80 mg/d in KINECT 3 or KINECT 4 were allowed one dose reduction to 40 mg/d; those unable to tolerate 40 mg/d were discontinued. The 6-week extension period of KINECT was excluded from the current long-term analysis because of the relatively shorter duration.

In the pooled DBPC population, which included participants from KINECT, KINECT 2, and KINECT 3, valbenazine dose groups were defined as follows: 40 mg/d (50 mg/d from KINECT [including the arm that initially received 100 mg/d for 2 weeks], 50 mg from KINECT 2, and 40 mg/d from KINECT 3) and 80 mg/d (75 mg/d from KINECT 2 and 80 mg/d from KINECT 3). KINECT 2 participants who received 25 mg/d (no escalation) were excluded. In the pooled long-term population, which included participants from KINECT 3 and KINECT 4, valbenazine dose groups were defined as follows: 40 mg/d (40 mg/d throughout KINECT 3 [DBPC and extension] and 40 mg/d from KINECT 4 [no dose escalation]) and 80 mg/d (80 mg/d throughout KINECT 3 [DBPC and extension] and 80 mg/d from KINECT 4 [with dose escalation at week 4]). Participants in KINECT 3 or KINECT 4 who had a dose reduction from 80 to 40 mg/d were included in the 80-mg/d group. KINECT 3 participants who initially received placebo and KINECT 4 participants who had no post–week 4 assessment were excluded.

Accounting for the shortened lifespan of patients with an SMI,[1,2] subgroups in this analysis were defined by age as follows: older (55 years or older) and younger (younger than 55 years).

2.2 | Assessments

The effects of treatment were evaluated using the Abnormal Involuntary Movement Scale (AIMS) and Clinical Global Impression of Change—Tardive Dyskinesia (CGI-TD). AIMS was scored by two central video raters who were blinded to treatment and study visit (KINECT, KINECT 2, and KINECT 3 [DBPC and extension]) or a qualified site rater (KINECT 4). Mean changes from baseline in AIMS total score (sum of items 1 to 7) were analyzed at week 6 (end of DBPC treatment), week 48 (end of long-term treatment), and week 52 (end of 4-week washout). The percentage of participants who met the AIMS threshold of response (greater than or equal to 50% total score improvement from baseline) was also analyzed. CGI-TD was scored by a site rater in all studies. CGI-TD analyses at weeks 6, 48, and 52 included mean score and the percentage of participants with an CGI-TD response (score of 1 ["very much improved"] or 2 ["much improved"]).

Psychopathology assessments included Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS) (schizophrenia/schizoaffective disorder participants); Young Mania Rating Scale (YMRS) and Montgomery-Åsberg Depression Rating Scale (MADRS) (mood disorder participants); and Columbia-Suicide Severity Rating Scale (C-SSRS) (all participants). Suicide-related treatment-emergent adverse events (TEAEs) were judged by the site investigator for severity, seriousness, and relationship to study drug.

TEAEs were documented at all study visits. Additional safety-related instruments included the Barnes Akathisia Rating Scale (BARS), Simpson Angus Scale (SAS), vital signs, and electrocardiogram (ECG). For ECG, the Fridericia formula was used for heart-rate–corrected QT interval ($QTcF = QT/RR^{1/3}$; RR = interval from onset of one QRS complex to onset of the next QRS complex).[26] In DBPC participants with an elevated QTcF (greater than 450 milliseconds) at baseline, mean changes from baseline to week 6 in QTcF were analyzed.

2.3 | Statistical analyses

Efficacy analyses were conducted in participants who received study drug and had available relevant assessments. For AIMS mean score change from baseline to week 6 and CGI-TD mean score at week 6, *P* values were based on linear contrasts from an analysis of covariance (ANCOVA) model, which included treatment, subgroup, treatment-by-subgroup interaction, and study as fixed effects and baseline AIMS total score as a covariate; treatment effect sizes were estimated using a Cohen's *d* calculation (least squares mean difference between each valbenazine treatment group and placebo, divided by the estimated common standard deviation). A mixed-model for repeated measures approach was not possible because of differences in trial designs (ie, no AIMS or CGI-TD assessment at week 4 in KINECT; no central rater AIMS at weeks 2 and 4 in KINECT 2). For comparisons between subgroups (55 years or older versus younger than 55 years), *P* values were based on a treatment-by-subgroup interaction (pooled DBPC population) or two-sample *t* test (pooled long-term population).

For AIMS and CGI-TD response at week 6, *P* values were based on the Pearson chi-square test. Numbers needed to treat (NNTs) were also calculated (1 divided by the difference in response rates [valbenazine − placebo]), with lower NNTs indicating that fewer additional patients were needed for a response to be observed. Comparisons between subgroups (55 years or older versus younger than 55 years) were based on the Breslow-Day test for homogeneity (pooled DBPC population) or chi-square test (pooled long-term group).

No significance testing between valbenazine and placebo was conducted for any safety outcome. However, numbers needed to harm (NNHs) were calculated for TEAEs (1 divided by the difference in TEAE incidence [valbenazine − placebo]), with higher NNHs indicating that more additional patients were needed for a TEAE with valbenazine to be observed. Additionally, comparisons between subgroups (55 years or older versus younger than 55 years) were analyzed for any TEAE, TEAEs leading to discontinuation, and serious TEAEs using the Breslow-Day test for homogeneity (pooled DBPC population) or chi-square test (pooled long-term population).

3 | RESULTS

3.1 | Participants

The pooled DBPC safety population had more older participants (55 years or older, n = 249) than younger participants (younger than 55 years, n = 178) (Table 1). Mean ages (±standard deviation [SD]) in the older and younger subgroups were 62.4 ± 6.1 years (range, 55 to 84 years) and 46.6 ± 6.5 years (range, 26 to 54 years), respectively (all treatment groups combined). Baseline characteristics in each subgroup (55 years or older, younger than 55 years) indicated that the older subgroup had fewer men (56.2%, 60.1%), more white participants (61.8%, 48.9%), and greater TD severity (AIMS total score, mean ± SD: 9.3 ± 4.3, 8.9 ± 4.0). Older and younger subgroups were similar in terms of psychiatric diagnosis (schizophrenia: 73.1%, 73.6%), psychiatric symptomatology (Brief Psychiatric Rating Scale total score, mean ± SD: 30.4 ± 7.2, 31.1 ± 8.0), and recent history of suicidality (prior 3 months: 4.0%, 3.4%). Lifetime history of suicidality was lower in the older versus younger participants (35.3%, 43.8%)

A majority of participants in both subgroups (55 years or older, younger than 55 years) reported a history of psychiatric disorders (69.5%, 62.9%), most commonly for insomnia (38.2%, 31.5%) and anxiety (28.1%, 22.5%) (Table S1). Medical histories reported by greater than or equal to 30% of both subgroups were metabolism/nutrition disorders (63.9%, 39.9%), vascular disorders (61.8%, 41.0%), gastrointestinal disorders (54.6%, 41.6%), musculoskeletal/connective tissue disorders (46.2%, 34.8%), and surgical/medical procedures (33.7%, 32.0%).

More than 80% of participants in both subgroups (55 years or older, younger than 55 years) were receiving one or more concomitant antipsychotic (81.5%, 88.2%), most commonly with quetiapine (21.7%, 25.3%) (Table S2). Other drug classes used concomitantly in greater

TABLE 1 Baseline characteristics by age subgroup (pooled DBPC safety population)

	Age <55 y			Age ≥55 y		
	Placebo (N = 75)	Valbenazine 40 mg/d (N = 60)	Valbenazine 80 mg/d (N = 43)	Placebo (N = 103)	Valbenazine 40 mg/d (N = 77)	Valbenazine 80 mg/d (N = 69)
Age, y						
Mean (SD)	46.2 (6.9)	47.5 (5.9)	46.2 (6.5)	62.8 (6.2)	61.6 (5.6)	62.6 (6.3)
Median (min, max)	48 (27, 54)	49 (26, 54)	48 (32, 54)	61 (55, 84)	61 (55, 77)	62 (55, 83)
Male, n (%)	44 (58.7)	40 (66.7)	23 (53.5)	58 (56.3)	44 (57.1)	38 (55.1)
Race, n (%)						
White	37 (49.3)	31 (51.7)	19 (44.2)	58 (56.3)	50 (64.9)	46 (66.7)
Black or African-American	35 (46.7)	25 (41.7)	22 (51.2)	39 (37.9)	24 (31.2)	22 (31.9)
Asian	0	0	0	0	1 (1.3)	0
Multiple or other	3 (4.0)	4 (6.7)	2 (4.7)	6 (5.8)	2 (2.6)	1 (1.4)
Body mass index, mean (SD), kg/m^2	29.3 (5.7)	28.1 (6.0)	30.3 (5.3)	27.5 (5.1)	28.5 (5.5)	26.8 (5.8)
Psychiatric diagnosis, n (%)						
Schizophrenia/schizoaffective disorder	57 (76.0)	50 (83.3)	24 (55.8)	77 (74.8)	59 (76.6)	46 (66.7)
Mood disorder	18 (24.0)	10 (16.7)	19 (44.2)	26 (25.2)	18 (23.4)	23 (33.3)
BPRS total score, mean (SD)	30.9 (7.9)	33.1 (8.1)	28.5 (7.6)	31.0 (7.5)	30.8 (7.8)	28.9 (6.1)
Suicidal ideation or behavior, n (%)[a]						
Lifetime history	29 (38.7)	33 (55.0)	16 (37.2)	36 (35.0)	24 (31.2)	28 (40.6)
Recent history, prior 3 months	2 (2.7)	4 (6.7)	0	3 (2.9)	5 (6.5)	2 (2.9)
AIMS total score, mean (SD)[b]	9.1 (3.9)	8.1 (4.2)	9.5 (4.0)	8.9 (4.9)	9.7 (4.1)	9.7 (3.4)

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale (at screening); DBPC, double-blind, placebo-controlled; SD, standard deviation.

[a]Based on the Columbia-Suicide Severity Rating Scale for suicidal ideation (score = 1 to 5) and suicidal behavior (score = 6 to 10). Participants only counted once for lifetime history and recent history based on their maximum score. No recent history of suicidal behavior was reported in either age subgroup (ie, all results for recent history represent suicidal ideation only).

[b]Based on scoring from central AIMS video raters who were blinded to treatment and study visit.

than or equal to 30% of participants in both subgroups were antidepressants (65.9%, 57.3%), antiepileptics (31.3%, 33.7%), and anticholinergics (30.5%, 40.4%).

3.2 | TD effects

At week 6 in the pooled DBPC population, mean improvements in AIMS total score were significantly greater with valbenazine 80 mg/d versus placebo in both subgroups (Figure 1A). Older participants also had a significantly greater improvement with valbenazine 40 mg/d. In the pooled long-term population, both subgroups showed AIMS improvement at week 48, with some return to baseline levels at week 52 (after 4-week washout). No significant differences between subgroups were found at weeks 6, 48, or 52.

The percentage of participants who met the threshold for AIMS response at week 6 (greater than or equal to 50% improvement from baseline) was higher for valbenazine 80 mg/d versus placebo in older participants (39.7% vs 9.7%, $P < .001$; NNT = 4) and younger participants (39.5% vs 10.8%, $P < .001$; NNT = 4) (Figure 1B). AIMS response for valbenazine 40 mg/d versus placebo was significant in the older subgroup (28.6% vs 9.7%, $P < .01$; NNT = 6) but not the younger subgroup (20.0% vs 10.8%,$P > .05$). Response rates at week 48 with valbenazine (combined doses) were 70.7% and 58.7% in the older and younger subgroups, respectively. Response rates decreased after 4-week washout in both subgroups. No significant differences between subgroups were found at weeks 6, 48, or 52.

On the basis of CGI-TD at week 6 in the pooled DBPC population, TD improvement was significantly greater with valbenazine 80 mg/d versus placebo in both subgroups (Figure 2A). Older participants also had significant improvement with valbenazine 40 mg/d. Mean CGI-TD scores for the pooled long-term population showed improvements in both subgroups at week 48, with a general loss of effect at week 52. There were no significant differences between subgroups except for valbenazine 40 mg/d at week 48 (55 years or older, 2.0; younger than 55 years, 2.5; $P < .05$), which indicated greater clinician-rated global improvement in older participants.

At week 6, the percentage of participants with a CGI-TD response (score 2 or less) for valbenazine 80 mg/d versus placebo was significant in the older subgroup (41.3% vs 19.4%, $P < .01$; NNT = 5) and younger subgroup (39.5% vs 18.5%, $P < .05$; NNT = 5) (Figure 2B). CGI-TD response was significant for valbenazine 40 mg/d versus placebo in younger participants (35.3% vs 18.5%, $P < .05$; NNT = 6) but

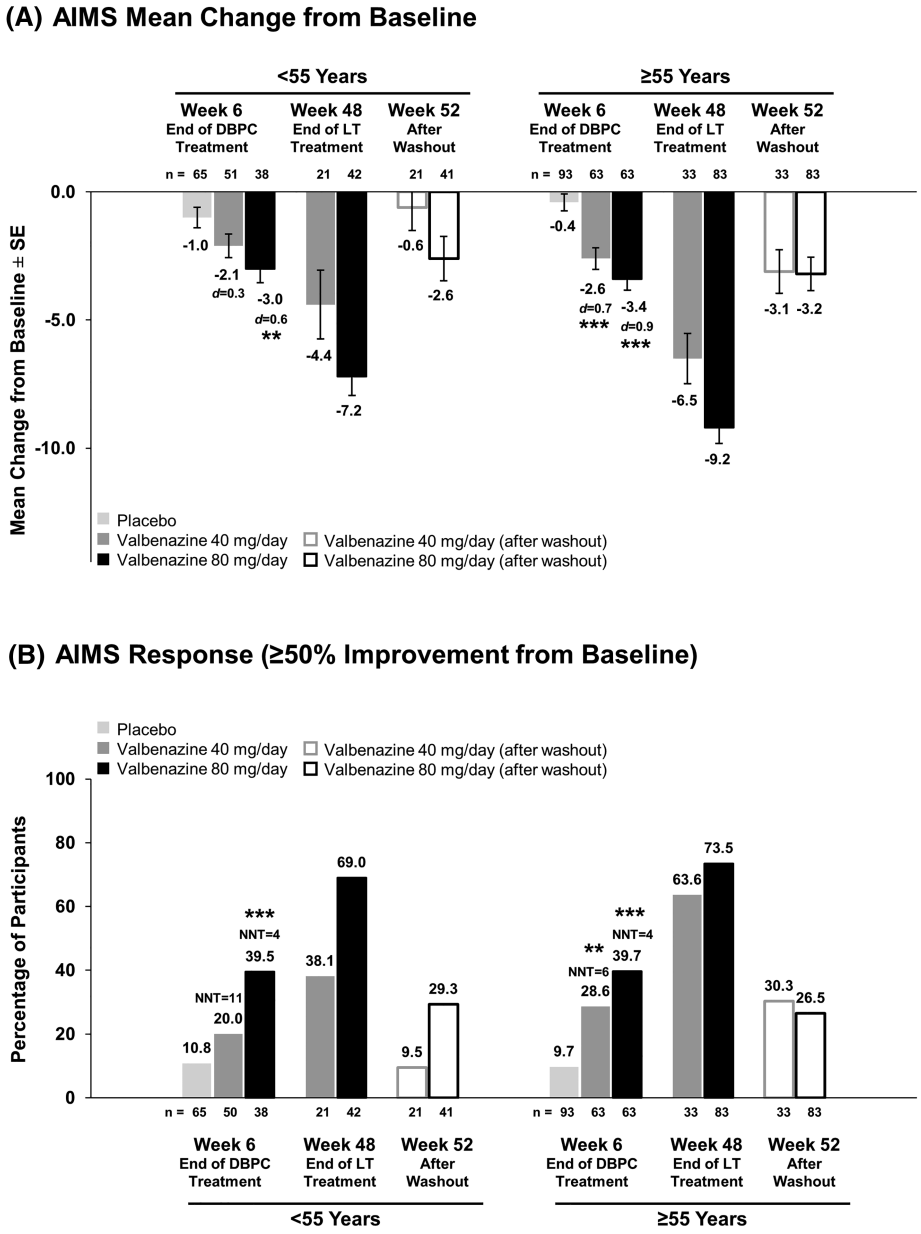

FIGURE 1 AIMS improvements by study visit: based on (A) mean change from baseline in AIMS total score and (B) percentage of participants with greater than or equal to 50% improvement in AIMS total score. Outcomes analyzed at week 6 in the pooled DBPC population (based on central-rater scoring only) and at weeks 48 and 52 in the pooled long-term population (based on central-rater scoring for KINECT 3 and site-rater scoring for KINECT 4), based on observed cases. Least squares means presented for week 6; means presented for weeks 48 and 52. $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$ versus placebo. AIMS, Abnormal Involuntary Movement Scale; *d*, Cohen's effect size; DBPC, double-blind placebo-controlled; NNT, number needed to treat; LT, long term; SE, standard error

not older participants (30.2% vs 19.4%, $P > .05$). Response rates at week 48 with valbenazine (combined doses) were 82.8% and 72.3% in the older and younger subgroups, respectively. Response rates decreased after 4 weeks in both subgroups. No significant differences between subgroups were found at weeks 6, 48, or 52.

3.3 | Psychopathology

Mean changes from baseline to weeks 6, 48, and 52 in psychiatric scale scores were minimal and not clinically significant in older or younger participants (Table 2; Table S3).

On the basis of available C-SSRS data, greater than 95% of the DBPC population had no suicidal ideation at baseline (55 years or older, 98.4% [241/245]; younger than 55 years, 97.7% [173/177]). Most of these participants continued to have no suicidal ideation at any time during treatment, both in the older subgroup (valbenazine, 97.9% [138/141]; placebo, 96.0% [96/100]) and younger subgroup (valbenazine, 98.0% [97/99]; placebo, 98.6% [73/74]). Among eight participants with nonactive or nonspecific suicidal ideation at baseline (C-SSRS score = 1 or 2), none had worsening in suicidal ideation during treatment. Similarly, most long-term study participants had no emergence of C-SSRS suicidal ideation (55 years or older, 93.5%

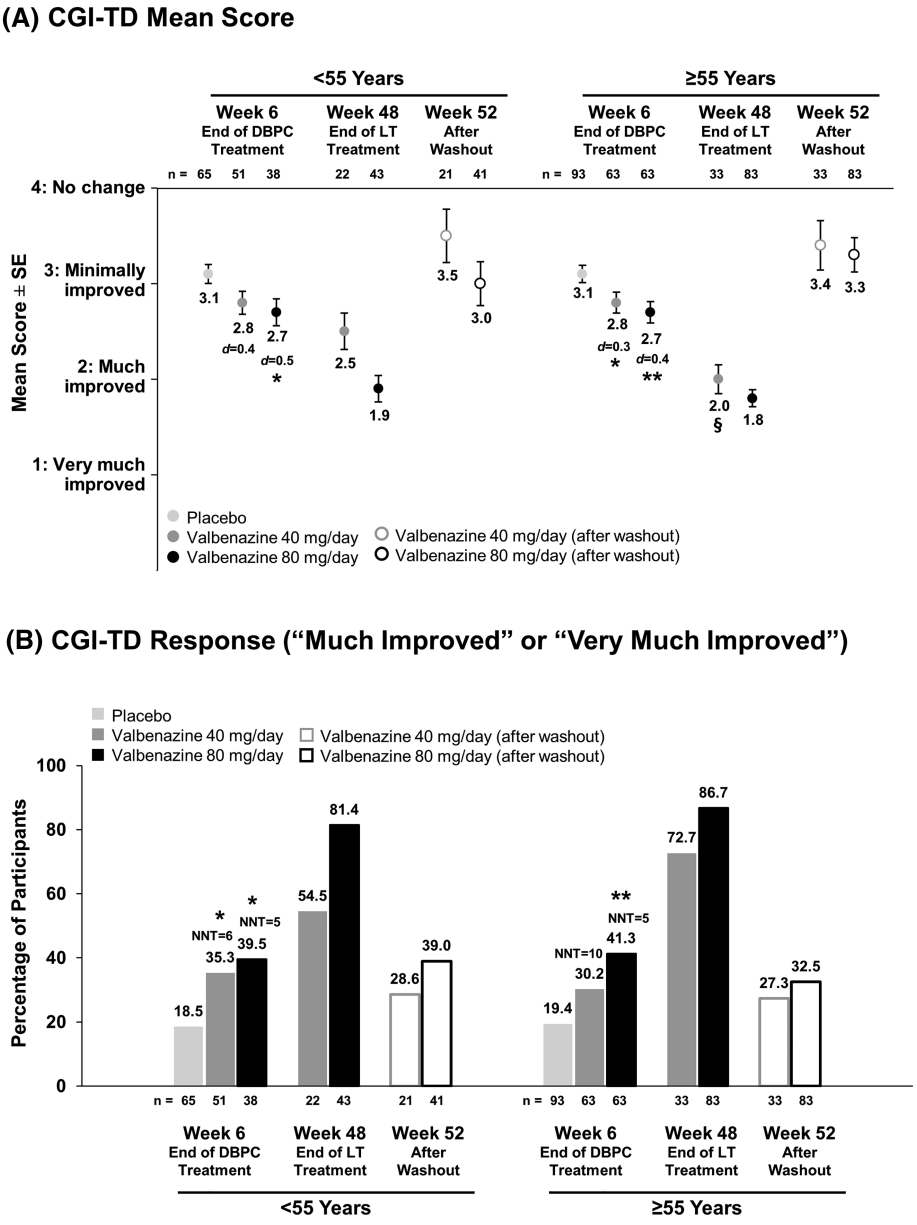

FIGURE 2 CGI-TD improvements by study visit: based on (A) CGI-TD mean scores and (B) percentage of participants with a CGI-TD score 2 or less. Analyzed at week 6 in the pooled DBPC population and at weeks 48 and 52 in the pooled long-term population, based on observed cases. Least squares means presented for week 6; means presented for weeks 48 and 52. $^{*}P < .05$; $^{**}P < .01$ versus placebo. $^{§}P < .05$ versus younger subgroup. CGI-TD, Clinical Global Impression of Change—Tardive Dyskinesia; *d*, Cohen's effect size; DBPC, double-blind, placebo-controlled; LT, long term; NNT, number needed to treat; SE, standard error

[173/185]; younger than 55 years, 92.8% [103/111]). None of the seven participants with nonactive, nonspecific, or active-without-intent suicidal ideation at baseline (C-SSRS score = 1 to 3) had any worsening during long-term treatment.

No DBPC participant had C-SSRS suicidal behavior (score = 6 to 10) at baseline or during treatment. Two suicidal behaviors were reported during long-term treatment: accidental overdose with clonazepam in a 36-year-old white man and aborted suicide attempt in a 55-year-old African-American woman experiencing visual and auditory hallucinations. Both participants exited the study; neither behavior was judged by the investigator as related to treatment.

3.4 | Adverse events

During DBPC treatment, no significant differences between older and younger valbenazine-treated participants were found for any TEAE, TEAEs leading to discontinuation, or serious TEAEs (Table 3). Five participants had a TEAE leading to dose reduction from 80 to 40 mg/d (55 years or older, n = 2; younger than 55 years, n = 3). No TEAE was reported in greater than or equal to 5% of all older valbenazine-treated participants; only somnolence (7.8%) and fatigue (6.8%) were reported in greater than or equal to 5% of all younger valbenazine-treated participants. In both subgroups, NNHs for TEAEs leading to discontinuation and serious TEAEs were greater than or

TABLE 2 Psychiatric symptom scales (pooled DBPC safety population)[a]

Available Assessments, n Mean Change from Baseline (SD)	Age <55 y Placebo	Valbenazine 40 mg/d	Valbenazine 80 mg/d	Age ≥55 y Placebo	Valbenazine 40 mg/d	Valbenazine 80 mg/d
PANSS total score	48 −0.2 (10.0)	44 −3.2 (6.3)	19 −0.1 (5.2)	69 −2.1 (7.1)	47 −1.0 (10.7)	41 −1.9 (6.1)
PANSS positive symptoms	48 −0.1 (3.8)	44 −1.3 (3.1)	19 0.2 (1.8)	69 −0.7 (2.5)	48 −0.4 (2.2)	41 −0.6 (1.6)
PANSS negative symptoms	48 −0.7 (3.3)	44 −0.2 (2.4)	19 0.9 (2.7)	69 −0.4 (3.0)	48 −0.3 (4.0)	41 −0.1 (2.8)
PANSS general psychopathology	48 0.6 (5.2)	44 −1.7 (3.9)	19 −1.2 (3.4)	69 −1.0 (3.7)	47 −0.4 (6.3)	41 −1.2 (3.9)
CDSS total score	48 −0.3 (2.7)	44 −0.8 (1.6)	19 −0.7 (1.8)	69 −0.3 (2.3)	48 −0.3 (2.3)	41 −0.5 (1.5)
YMRS total score	17 0.2 (3.2)	10 −0.7 (2.5)	18 −0.7 (1.8)	25 0.2 (2.0)	15 0.1 (2.8)	23 −2.1 (2.6)
MADRS total score	17 0.5 (6.8)	10 −0.1 (3.9)	18 −2.1 (4.1)	25 0.7 (3.1)	15 −0.2 (4.4)	23 −1.4 (4.4)

Abbreviations: CDSS, Calgary Depression Scale for Schizophrenia; DBPC, double-blind, placebo-controlled; MADRS, Montgomery-Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; YMRS, Young Mania Rating Scale.

[a]PANSS and CDSS administered to participants with schizophrenia/schizoaffective disorder; MADRS and YMRS administered to participants with a mood disorder.

TABLE 3 Adverse events by age subgroup (pooled DBPC safety population)

	Age <55 y Placebo (N = 75)	Valbenazine 40 mg/d (N = 60)	Valbenazine 80 mg/d (N = 43)	Age ≥55 y Placebo (N = 103)	Valbenazine 40 mg/d (N = 77)	Valbenazine 80 mg/d (N = 69)
Summary, n (%)						
Any TEAE, n (%)	33 (44.0)	21 (35.0)	21 (48.8)	38 (36.9)	35 (45.5)	32 (46.4)
NNH[a]		−11	20		11	10
TEAE leading to discontinuation, n (%)	2 (2.7)	0	2 (4.7)	6 (5.8)	5 (6.5)	3 (4.3)
NNH[a]		−37	50		149	−67
Serious TEAE	3 (4.0)	0	3 (7.0)	3 (2.9)	6 (7.8)	3 (4.3)
NNH[a]		−25	33		20	69
Death	0	0	0	1 (1.0)[b]	0	1 (1.4)[b]
TEAEs by preferred term, n (%)[c]						
Headache	1 (1.3)	4 (6.7)	1 (2.3)	3 (2.9)	1 (1.3)	4 (5.8)
Somnolence	2 (2.7)	7 (11.7)	1 (2.3)	2 (1.9)	3 (3.9)	3 (4.3)
Vomiting	1 (1.3)	1 (1.7)	3 (7.0)	0	1 (1.3)	1 (1.4)
Fatigue	3 (4.0)	5 (8.3)	2 (4.7)	0	2 (2.6)	1 (1.4)
Urinary tract infection	4 (5.3)	1 (1.7)	0	4 (3.9)	4 (5.2)	1 (1.4)
Akathisia	1 (1.3)	0	3 (7.0)	0	3 (3.9)	0
Suicidal ideation	1 (1.3)	0	1 (2.3)	3 (2.9)	4 (5.2)	0
Dry mouth	3 (4.0)	2 (3.3)	0	0	6 (7.8)	0

Abbreviations: DBPC, double-blind, placebo-controlled; NNH, number needed to harm; TEAE, treatment-emergent adverse event.

[a]Negative number needed to harm indicates lower incidence for valbenazine versus placebo.

[b]Due to cardiopulmonary arrest (placebo) and possible cardiovascular event (valbenazine 80 mg/d); neither judged as related to treatment.

[c]Reported in greater than or equal to 5% of participants in any treatment group in either age subgroup.

equal to 20 or negative (ie, lower incidence with valbenazine vs placebo). No TEAE led to discontinuation in more than two valbenazine-treated participants in either subgroup. No serious TEAE was reported in more than one valbenazine-treated participant in either subgroup.

During long-term treatment, a significant difference between subgroups (55 years or older, younger than 55 years; $P < .05$) was found for any TEAE (76.8%, 63.2%), TEAE leading to discontinuation (18.9%, 9.6%), and serious TEAE (20.5%, 10.5%) (Table S4). TEAEs reported in greater than or equal to 5% of all older participants were headache (10.0%), somnolence (8.9%), urinary tract infection (8.9%), dizziness (6.3%), fatigue (5.8%), suicidal ideation (5.8%), and nasopharyngitis (5.3%). TEAEs reported in greater than or equal to 5% of all younger participants were urinary tract infection (8.8%), headache (7.0%), fatigue (7.0%), somnolence (6.1%), vomiting (6.1%), suicidal ideation (5.3%), and dizziness (5.3%).

Four deaths occurred during the studies; none were related to treatment. Two occurred during DBPC treatment because of cardiopulmonary arrest (placebo) and possible cardiovascular event (valbenazine 80 mg/d). Two occurred during long-term treatment because of multiple causes (hyperkalemia, cardiac failure, hepatic failure, diabetes mellitus, metabolic acidosis, and pleural effusion) and breast cancer (both valbenazine 80 mg/d).

3.5 | Additional safety outcomes

No notable changes from baseline were found in BARS (akathisia) or SAS (parkinsonism) scores at weeks 6, 48, or 52 (Table 4, Table S5). Supine vital signs and ECG parameters were also generally stable throughout the study (Table 4, Table S5). In DBPC participants who had an elevated QTcF (greater than 450 milliseconds) at baseline, those receiving valbenazine had a mean decrease in QTcF at week 6 (55 years or older, −8.9 milliseconds [n = 3]; younger than 55 years, −15.2 milliseconds [n = 2]); those receiving placebo had a mean increase (55 years or older, 9.3 milliseconds [n = 2]; younger than 55 years, 24.7 milliseconds [n = 1]).

TABLE 4 Movement scales, vital signs, and electrocardiogram (pooled DBPC safety population)

	Age <55 y			Age ≥55 y		
FL Mean Change from Baseline (SD)	Placebo	Valbenazine 40 mg/d	Valbenazine 80 mg/d	Placebo	Valbenazine 40 mg/d	Valbenazine 80 mg/d
Movement Scales						
BARS total score	65 −0.4 (1.8)	54 0.1 (1.7)	37 −0.4 (1.6)	94 −0.5 (1.5)	63 −0.2 (1.8)	64 −0.5 (1.6)
BARS global score	65 −0.1 (0.9)	54 0.1 (0.7)	37 −0.1 (0.9)	94 −0.1 (0.6)	63 −0.1 (1.0)	64 −0.3 (0.8)
SAS total score	65 −0.0 (0.2)	54 −0.1 (0.2)	37 −0.1 (0.2)	94 −0.1 (0.3)	63 −0.1 (0.2)	64 −0.1 (0.2)
Supine vital signs and weight						
Heart rate, bpm	65 −0.6 (9.8)	53 −4.0 (10.7)	37 −0.9 (11.6)	94 −2.4 (8.2)	63 −1.6 (13.5)	64 −2.1 (11.4)
Systolic blood pressure, mmHg	65 −0.5 (12.8)	53 −2.2 (11.4)	37 −2.4 (11.8)	94 0.7 (12.9)	63 −1.1 (12.5)	64 −1.4 (17.1)
Diastolic blood pressure, mmHg	65 0.7 (11.4)	53 −2.2 (8.6)	37 −0.8 (8.4)	94 −0.6 (9.0)	63 −1.5 (7.9)	64 −1.4 (10.4)
Body weight, kg	65 0.1 (2.3)	53 0.2 (2.4)	37 0.7 (2.4)	94 0.2 (1.9)	63 0.2 (2.5)	64 0.3 (1.8)
Electrocardiogram						
Heart rate, bpm	65 0.5 (10.4)	54 −2.0 (11.8)	37 −1.4 (8.9)	93 −1.0 (10.1)	63 −2.4 (12.5)	64 −4.5 (11.4)
PR interval, ms	65 −0.1 (13.1)	53 0.6 (11.4)	37 1.7 (9.4)	91 −1.7 (15.0)	63 0.3 (10.0)	64 2.4 (16.5)
QRS duration, ms	65 0.3 (5.6)	54 −1.4 (6.7)	37 −1.8 (5.6)	93 0.0 (7.6)	63 −0.5 (5.4)	64 −0.2 (8.7)
QT interval, ms	65 −0.1 (22.9)	54 5.2 (29.7)	37 4.6 (18.3)	93 3.0 (23.8)	63 5.0 (28.2)	64 10.1 (27.1)
QTcF interval, ms	65 0.8 (11.8)	54 1.4 (17.8)	37 1.1 (14.9)	93 1.6 (15.2)	63 1.7 (15.5)	64 2.6 (15.1)

Abbreviations: BARS, Barnes Akathisia Rating Scale; DBPC, double-blind, placebo-controlled; QTcF, Fridericia correction; SAS, Simpson Angus Scale; SD, standard deviation.

4 | DISCUSSION

To our knowledge, this is the first analysis of a Food and Drug Administration (FDA)-approved TD medication in older patients. Valbenazine clinical trials were well suited to this analysis because of the relatively large number of older participants (55 years or older) enrolled in these trials (DBPC, n = 249; long-term, n = 190). Data pooled from three DBPC and two long-term studies indicate that older and younger TD patients responded favorably to once-daily valbenazine. On the basis of the AIMS response in placebo-controlled trials (greater than or equal to 50% total score improvement from baseline to week 6), the older subgroup had NNTs of 4 and 6 for valbenazine 80 and 40 mg/d, respectively. The corresponding NNT numbers for the younger subgroup were 4 and 11. On the basis of CGI-TD response (rating of "much improved" or "very much improved" at week 6), both older and younger subgroups had an NNT of 5 for valbenazine 80 mg/d. For valbenazine 40 mg/d, the older and younger subgroups had NNTs of 10 and 6, respectively. The type of measure used (ie, AIMS vs CGI-TD) may have had an impact on these NNT outcomes. Collectively, however, these results indicate that both older and younger participants had clinically meaningful improvements with valbenazine. Moreover, the anti-dyskinetic effects of valbenazine did not appear to be compromised by the emergence of other movement disorders, as indicated by the minimal changes from baseline in BARS and SAS scores.

TD may have a profound functional effect in older patients, including an increased likelihood of falls in a population that already has a higher risk of falls because of balance and gait problems. TD may also interfere with instrumental activities of daily living such as eating, bathing, and dressing. Disability from TD may compound the effects of medical morbidity and reduced independence seen in older people with SMI. Since functional measures have not been included in treatment studies of TD,[22,23,27,28] future research is needed to better understand the effects of treatment on daily functioning and health-related quality of life.

An important goal in the valbenazine studies was to treat TD without compromising psychiatric stability. The studies included patients with well-managed psychiatric symptoms, and psychotropic medications needed to maintain stability were allowed. In both older and younger participants, mean score changes from baseline in psychiatric symptom scales (PANSS, CDSS, YMRS, and MADRS) were minimal throughout DBPC and long-term treatment. Some suicidal ideation and behavior were reported, as might be expected given the lifetime history of suicidality in these study populations. However, valbenazine did not appear to worsen suicidal ideation or behavior in older or younger participants.

One concern when medicating older patients is the increased potential for adverse effects. In the DBPC studies, NNHs for discontinuation due to a TEAE and serious TEAE were similar between older and younger subgroups. An earlier analysis found that valbenazine was approximately 15 times more likely to result in a treatment response than in discontinuation due to a TEAE.[29] In the current analysis, the NNH for discontinuation due to a TEAE was −67 for valbenazine 80 mg/d in older participants, reflecting the lower incidence with valbenazine versus placebo (4.3% vs 5.8%). However, on the basis of the NNH for serious TEAE and the NNT for AIMS response, older participants who received valbenazine 80 mg/d had a risk/benefit ratio that indicated that this dose was approximately 17 times more likely to help than harm (NNH/NNT = 69/4 = 17.3). The risk/benefit ratio was lower for valbenazine 40 mg/d (NNH/NNT = 20/6 = 3.3). However, since the actual number of participants with a serious TEAE was low in all treatment groups (80 mg/d, n = 3; 40 mg/d, n = 6; placebo, n = 3), no strong conclusions can be drawn regarding the risk/benefit of 80 mg/d over 40 mg/d. Both doses showed a favorable NNH/NNT profile that was consistent with previous reports.[29]

As is typical for clinical trials, the valbenazine studies required that patients be medically stable before enrollment. Stability appeared to be maintained, as indicated by the generally small mean changes in biological measures (body mass index, vital signs, and ECG) and movement scales (BARS and SAS) in both older and younger participants. However, older patients in clinical trials can experience more adverse effects over time. In the long-term studies, the incidence of TEAEs was significantly higher in the older subgroup, possibly because of various age-associated factors such as changes in metabolism, multiple comorbidities, and chronic exposure to multiple medications including antipsychotics.[30,31] However, no new TEAEs of clinical concern were found in the older subgroup, and no laboratory TEAE (liver enzyme increase, creatine phosphokinase increase, prolactin increase, glucose increase, and triglyceride increase) occurred in more than two older participants at any time during long-term treatment except for blood creatine increase (four participants) and gamma-glutamyltransferase increase (three participants). These results suggest that older patients taking valbenazine likely do not require additional physical monitoring beyond usual care for chronic medical conditions.

The main limitation of this analysis is its post hoc nature since none of the studies were specifically designed to evaluate the effects of valbenazine by age. Additionally, the older subgroup was relatively "young" (mean/median age, 62/61 years), and patients with significant or unstable medical illnesses were excluded. Finally, the valbenazine trials did not include functional measures, and more research is needed to understand the social and functional impact of TD on the lives of older patients. However, by characterizing the effects of valbenazine in older patients with an SMI, this analysis offers information that may be clinically applicable.

5 | CONCLUSION

In sum, valbenazine appears to have similar and clinically meaningful TD improvements in both older and younger patients, with no apparent additional safety concerns in older patients. The TD response of older adults to valbenazine was demonstrated with NNTs ranging from 4 to 10, depending on the dose and instrument for rating. This analysis indicates that valbenazine may be used to reduce TD symptoms in patients regardless of age while allowing the continuation of psychiatric/antipsychotic treatment.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data that support the findings in this report are available from Neurocrine Biosciences, Inc. All reasonable requests for data will be considered.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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