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Research paper

# The effects of valbenazine on tardive dyskinesia in patients with a primary mood disorder

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ABSTRACT

*Background:* Few studies have assessed the treatment of tardive dyskinesia (TD) in patients with primary mood disorders who are managed with antipsychotics. The effects of once-daily valbenazine on TD were evaluated in adults with a bipolar or depressive disorder.

*Methods:* Data were pooled from two 6-week double-blind placebo-controlled trials (KINECT 2 and KINECT 3; 114 mood participants) and a long-term blinded extension study (KINECT 3 extension; 77 mood participants) of valbenazine in adults with TD. Efficacy assessments included Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1–7), Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD), and Patient Global Impression of Change (PGIC). Safety assessments included treatment-emergent adverse events (TEAEs), Young Mania Rating Scale, and Montgomery–Åsberg Depression Rating Scale.

*Results:* At Week 6, mean improvements in AIMS total score were significantly greater with valbenazine versus placebo (40 mg/day, −3.1 [$P < 0.01$]; 80 mg/day, −3.5 [$P < 0.001$]; placebo, −0.9). Significant differences between valbenazine (80 mg/day) and placebo were also found for Week 6 AIMS response (≥50% total score improvement) and CGI-TD response ("much improved" or "very much improved"), but not PGIC response. Sustained improvements in AIMS, CGI-TD, and PGIC were found through 48 weeks. Valbenazine was generally well tolerated, with no unexpected TEAEs, worsening in psychiatric symptoms, or emergence of suicidality.

*Limitations:* Pooled analyses were conducted post hoc, and neither study was designed to focus solely on mood disorder patients.

*Conclusions:* In participants with primary mood disorders, once-daily treatment with valbenazine was generally well tolerated and resulted in 6-week and sustained TD improvements.

## 1. Introduction

Tardive dyskinesia (TD), a persistent and often debilitating involuntary movement disorder affecting the face, mouth, trunk, limbs, and/or extremities, is associated with prolonged exposure to dopamine receptor blocking agents (DRBAs), such as antipsychotics (Caroff et al., 2011a; Rana et al., 2013; Vijayakumar and Jankovic, 2016; Waln and Jankovic, 2013). Second-generation (atypical) antipsychotics were initially anticipated to be less likely to cause TD than first-generation antipsychotics; however, evidence indicates that the risk of developing TD with both first- and second-generation antipsychotics remains an important treatment consideration (Bhidayasiri et al., 2013; Carbon et al., 2017; Caroff et al., 2011b; Cloud et al., 2014; Peluso et al., 2012; Woods et al., 2010). In a recent meta-analysis of 41 clinical studies, the prevalence of TD was 30.0% in patients receiving first-generation antipsychotics and 20.7% in patients receiving second-generation antipsychotics, demonstrating that the introduction of second-generation antipsychotics had not eliminated the risk of TD (Carbon et al., 2017).

In addition, expanded use of atypical antipsychotics in patients with diagnoses other than schizophrenia or related psychotic disorders (i.e., those with a primary diagnosis of bipolar disorder, major depressive disorder [MDD], or other related mood disorder) has contributed to the rising number of patients with TD (Cloud et al., 2014). Many patients with non-psychotic mood disorders are highly functional, and therefore

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may have higher levels of awareness and distress from even relatively less noticeable abnormal movements than patients with schizophrenia (Daniel et al., 2016). Against this background of increased atypical antipsychotic use in patients with mood disorders, the greater potential for negative impact of movement-related side effects in mood disorder populations—along with the recognition that mood disorders are themselves an independent risk factor for TD (Kane, 1999; Keck et al., 2000)—provides the rationale for evaluating TD response outcomes in persons with mood disorders receiving TD treatment.

In 2017, the US Food and Drug Administration (FDA) approved valbenazine for the treatment of TD in adults. Valbenazine is a novel and highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor with an approximately 20-hour half-life and low peak-to-trough concentration ratio that allows for once-daily dosing (Grigoriadis et al., 2017; Thai-Cuarto et al., 2018). The efficacy and safety of valbenazine were demonstrated in two 6-week, double-blind, placebo-controlled trials (KINECT 2 [NCT01733121], KINECT 3 [NCT02274558]) (Hauser et al., 2017; O'Brien et al., 2015). Long-term tolerability and sustained TD improvements were demonstrated in the KINECT 3 extension study, which included patients who continued blinded valbenazine treatment for an additional 42 weeks (Factor et al., 2017).

Both KINECT 2 and KINECT 3 included patients with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnosis of schizophrenia, schizoaffective disorder, or any mood disorder. While both studies conducted a priori analyses of efficacy by underlying diagnosis, neither study was designed or powered for statistical testing within the mood diagnosis subgroup. The pooled data from these studies were analyzed post hoc to further characterize this patient population and evaluate their response to treatment with valbenazine.

## 2. Methods

### 2.1. Study design and participants

Methods of the individual studies have been previously reported (Factor et al., 2017; Hauser et al., 2017; O'Brien et al., 2015). In summary, participants in KINECT 2 were randomized to receive 6 weeks of once-daily placebo or valbenazine (25–75 mg escalated in 25 mg increments depending on TD symptoms and tolerability; Supplementary Fig. S1). Participants in KINECT 3 received placebo, valbenazine 40 mg/day, or valbenazine 80 mg/day (Hauser et al., 2017) for 6 weeks, with the option to enter a 42-week extension period followed by a 4-week washout period. During the extension period, participants received blinded daily doses of 40 mg/day or 80 mg/day valbenazine (Factor et al., 2017). A dose reduction from 80 mg/day to 40 mg/day was allowed in both studies for tolerability; participants who were unable to tolerate valbenazine 40 mg/day were discontinued from the study.

The studies included medically and psychiatrically stable adults with schizophrenia, schizoaffective disorder, or any mood disorder and moderate or severe antipsychotic-induced TD per qualitative assessment by an external reviewer at screening. Stable doses of concomitant medication to treat existing psychiatric and other medical disorders were allowed throughout the studies.

The pooled double-blind placebo-controlled population included participants from KINECT 2/KINECT 3 who had a primary mood disorder, including bipolar disorder and MDD. The long-term population included participants from the KINECT 3 extension study who had a primary mood disorder. The pooled 40 mg/day group included participants who received 40 mg/day (KINECT 3) or 50 mg/day (KINECT 2), and the 80 mg/day group included participants who received 75 mg/day (KINECT 2) or 80 mg/day (KINECT 3). One KINECT 2 mood participant who received 25 mg/day (i.e., no dose escalation to 50 or 75 mg/day) was excluded from the post hoc analyses.

### 2.2. Efficacy

In the pooled double-blind placebo-controlled and long-term populations, efficacy was evaluated in participants who received ≥1 dose of study drug and had an available assessment at the relevant study visit (Week 6, Week 48, or Week 52). Assessments included the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976), Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) (Guy, 1976), and Patient Global Impression of Change (PGIC) (Guy, 1976).

For the AIMS, scoring of items 1–7 was based on the consensus rating between 2 central video raters (movement disorder specialists) who were blinded to treatment and study visit. Central video raters used the following anchors for scoring items 1–7: (0) no dyskinesia; (1) minimal or slight dyskinesia: low amplitude, present during some but not most of the exam; (2) mild dyskinesia: low amplitude and present during most of the exam (or moderate amplitude and present during some of exam); (3) moderate dyskinesia: moderate amplitude and present during most of exam; (4) severe dyskinesia: maximal amplitude and present during most of exam. AIMS total score was defined as the sum score of items 1–7.

Mean change in AIMS total score was assessed from baseline to Week 6 in the pooled double-blind population, and from baseline to Weeks 8, 16, 32, 48 (end of long-term treatment), and 52 (end of washout) in the long-term population. Mean changes from baseline to Week 6 were analyzed using an analysis of covariance (ANCOVA) model with treatment groups and study as fixed effects and baseline AIMS total score as a covariate. Statistical differences between valbenazine (40 mg/day, 80 mg/day) and placebo were based on LS mean differences, with treatment effect sizes estimated using Cohen's *d*. AIMS response, defined as ≥50% total score improvement from baseline, was assessed at Week 6 (pooled double-blind population) and at Weeks 48 and 52 (long-term population). Additional efficacy measures included CGI-TD and PGIC mean scores and response (score ≤ 2 [“very much improved” or “much improved”]) at Weeks 6, 48, and 52. Mean CGI-TD and PGIC scores at Week 6 were analyzed using an analysis of variance (ANOVA) that included treatment groups and study as variables. Statistical differences between valbenazine (40 mg/day, 80 mg/day) and placebo were based on LS mean differences, with treatment effect sizes estimated using Cohen's *d*. Analyses of response (AIMS, CGI-TD, PGIC) included numbers needed to treat (NNTs) and odds ratios (ORs) with 95% confidence intervals (95% CIs); statistical differences between valbenazine and placebo were analyzed using the Pearson chi-square test. Long-term outcomes (Weeks 48 and 52) were analyzed descriptively.

### 2.3. Subgroup analyses

To explore the potential effects of baseline characteristics on TD improvements, AIMS mean score changes from baseline to Week 6 and Week 48 were analyzed descriptively in the following subgroups: age (<65 years, ≥65 years), sex (male, female), body mass index (BMI, <25 kg/m$^2$, 25 to <30 kg/m$^2$, ≥30 kg/m$^2$), history of substance abuse (yes, no), antidepressant medication use (selective serotonin reuptake inhibitor [SSRI], serotonin and norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA] or other antidepressant, none), antipsychotic use (yes, no), anticholinergic medication use (yes, no), and benzodiazepine use (yes, no).

### 2.4. Safety

Safety was assessed in participants who received ≥1 dose of study drug. Assessments included treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital sign measurements, and electrocardiograms (ECGs). Emergence of suicidal ideation or behavior was monitored using the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). Psychiatric status was monitored using the Young

**Table 1**
Baseline characteristics.

| | Placebo ($n$ = 44) | Valbenazine 40 mg/day ($n$ = 28) | Valbenazine 80 mg/day ($n$ = 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) |
| 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, $n$ (%)[c] | | | |
| 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) |

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.

[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.

[c] Based on endorsement of Columbia-Suicide Severity Rating Scale items 1–10.

Mania Rating Scale (YMRS) (Young et al., 1978) and Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). The Barnes Akathisia Rating Scale (BARS) (Barnes, 1989) and Simpson Angus Scale (SAS) (Simpson and Angus, 1970) were administered to evaluate treatment-emergent akathisia and parkinsonism, respectively.

## 3. Results

The pooled double-blind mood population included 114 participants (placebo, $n$ = 44, 40 mg/day, $n$ = 28, 80 mg/day, $n$ = 42); the long-term population included 77 participants (40 mg/day, $n$ = 36, 80 mg/day, $n$ = 41). Baseline characteristics in the double-blind population were generally similar across treatment groups (Table 1). Bipolar disorder was the primary diagnosis in 60.5% (69/114) of participants; of these, 27.5% (19/69) also had a history of substance abuse. More than 30% of participants with bipolar disorder or depression/major depression had a history of gastroesophageal reflux disease, anxiety, insomnia, and hypertension (Supplementary Table S1).

At baseline, 62.3% (71/114) of all mood participants were taking a concomitant antipsychotic medication (Table 1); of these, 90.1% (64/71) were taking an atypical antipsychotic only. Medication history indicated greater use of anticholinergic agents, antiepileptics, antipsychotics, and anxiolytics in participants with bipolar disorder relative to those with depression/major depression (Supplementary Table S2); depressed participants had greater use of antidepressants and hypnotics/sedatives.

### 3.1. Efficacy

In the pooled double-blind mood population, mean improvements from baseline to Week 6 in AIMS total score were significantly greater with valbenazine (40 and 80 mg/day) versus placebo (Fig. 1A). Cohen's $d$ treatment effect sizes were 0.72 and 0.84 for valbenazine 40 and 80 mg/day, respectively. Mood disorder participants who entered the KINECT 3 extension study showed continued improvements throughout 48 weeks of treatment (Fig. 1B). After washout, mean AIMS scores reverted toward baseline levels, indicating some loss of treatment effect.

The analysis of AIMS total score improvements from baseline to Week 6 by subgroup showed greater improvement with one or both doses of valbenazine relative to placebo in all subgroups (Supplementary Table S3). Improvements were generally sustained through Week 48.

At Week 6, a significantly higher proportion of mood participants in the pooled double-blind population had an AIMS response (≥50% total score improvement from baseline) with valbenazine 80 mg/day versus placebo (37.5% vs 11.9%, $P < 0.01$; Fig. 2A). NNTs for AIMS response were 6 and 4 for valbenazine 40 and 80 mg/day, respectively. After long-term treatment with valbenazine 40 or 80 mg/day, 46.5% of all mood participants had an AIMS response. Response rates decreased after washout, although some participants in both dose groups maintained a ≥ 50% decrease from baseline in AIMS total score.

Mean CGI-TD scores at Week 6 indicated significantly greater global improvements with valbenazine versus placebo ($P < 0.01$, both doses), and Cohen's $d$ treatment effect sizes were 0.73 and 0.80 for valbenazine 40 and 80 mg/day, respectively (Fig. 3A). Mean PGIC scores for

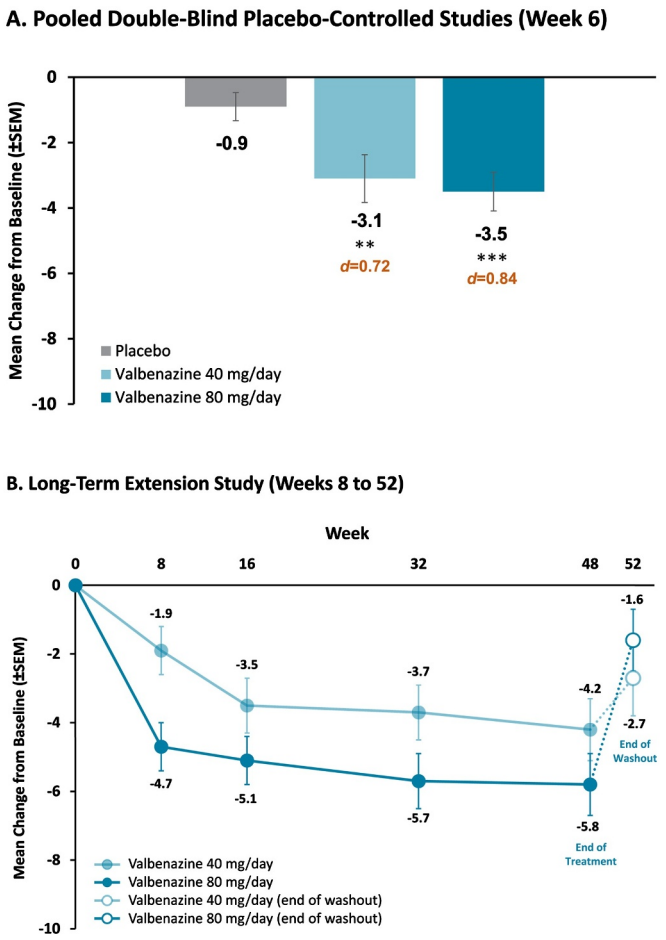


**Fig. 1.** AIMS total score mean changes from baseline. $^{**}P < 0.01$; $^{***}P < 0.001$ versus placebo. Based on least squares mean differences between valbenazine and placebo: 40 mg/day, −2.2; 80 mg/day, −2.6. AIMS, Abnormal Involuntary Movement Scale; *d*, Cohen's effect size; SEM, standard error of the mean.

valbenazine were also improved versus placebo, but the improvement did not reach statistical significance and Cohen's *d* values indicated minimal treatment effect (Fig. 3B). For both CGI-TD and PGIC, a trend toward greater improvement was found at Week 48 with loss of effect at Week 52 (after drug-free washout).

At Week 6, a significant difference between valbenazine 80 mg/day and placebo was found for CGI-TD response ($P < 0.01$), with an NNT of 4 (Fig. 2B). Global response rates (CGI-TD and PGIC) were higher at Week 48 compared to Week 6, with decreases following washout (Week 52) that were greater for CGI-TD response than PGIC response (Fig. 2B and C).

### 3.2. Safety

In the pooled double-blind population, the incidence of any TEAE was higher with valbenazine versus placebo (Table 2). One participant had a serious TEAE (40 mg/day), and 2 discontinued due to a TEAE (both 40 mg/day). The only TEAE reported in ≥10% of all valbenazine-treated participants was somnolence (11.4% [8/70]). In the long-term extension study, the only TEAE reported in ≥10% of all valbenazine-treated participants was headache (10.4% [8/77] (Supplementary Table S4). No deaths occurred in participants with a mood disorder during the double-blind trials or the long-term extension study.

Of 113 participants in the double-blind population with available C-SSRS data and no suicidal ideation at baseline (score = 0), 109 (96.5%) continued to have no suicidal ideation at any time during the study. Three participants (placebo, $n = 1$; 40 mg/day, $n = 2$) shifted to a score

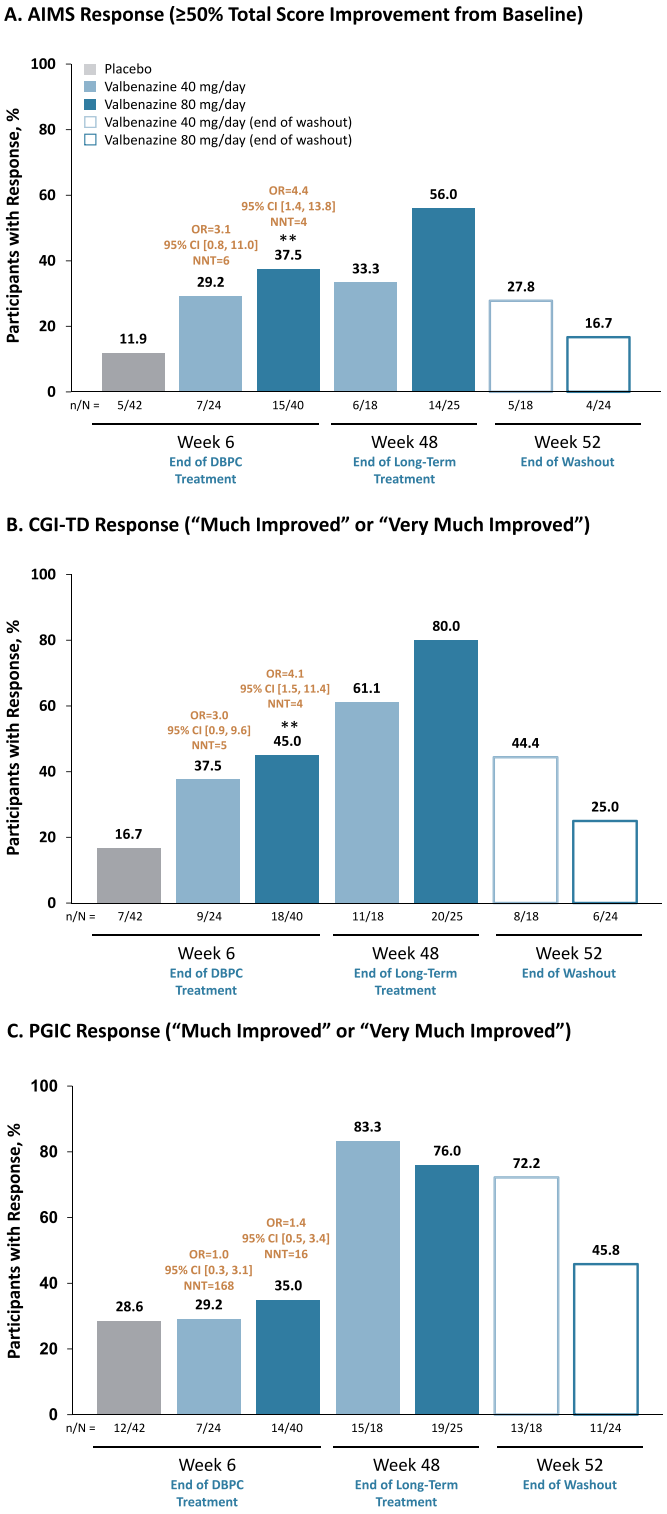


**Fig. 2.** AIMS, CGI-TD, and PGIC response. $^{**}P < 0.01$ versus placebo. AIMS, Abnormal Involuntary Movement Scale; CI, confidence interval; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; DBPC, double-blind placebo-controlled; NNT, number needed to treat; OR, odds ratio; PGIC, Patient Global Impression of Change.

of 1 ("wish to be dead"), and one participant (placebo) shifted to a score of 2 ("non-specific active suicidal thoughts"). One participant who had suicidal ideation at baseline (80 mg/day, score = 1) did not have any ideation during treatment.

No notable worsening from baseline in psychiatric scales scores

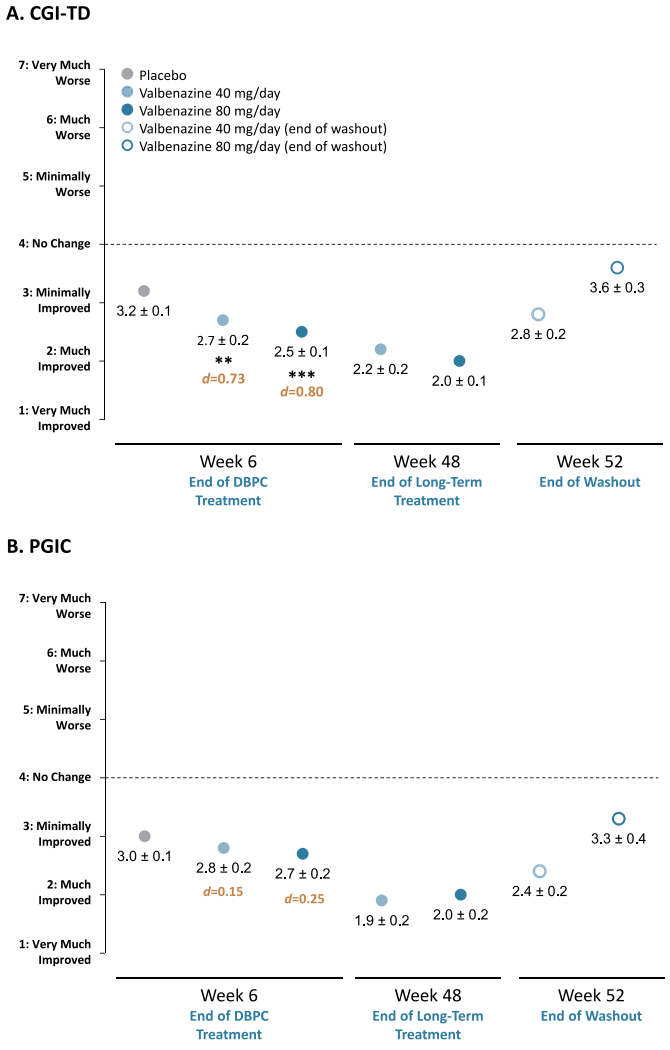


**Fig. 3.** CGI-TD and PGIC mean scores. Mean scores ( ± standard error of the mean) are presented. $^{**}P < 0.01$; $^{***}P < 0.001$ versus placebo. Based on least squares mean differences between valbenazine and placebo for CGI-TD (40 mg/day, − 0.6; 80 mg/day, − 0.7) and PGIC (40 mg/day, − 0.1; 80 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.

(YMRS, MADRS) was found at Weeks 6, 48, or 52 (Fig. 4). Mean changes from baseline in movement scale scores (BARS, SAS), vital signs, ECG parameters, and key laboratory parameters were minimal (Supplementary Table S5).

## 4. Discussion

The insufficient body of evidence on the effects of TD treatment in adults with mood disorders provided the impetus for conducting this post hoc analysis. Pooling the data from mood disorder participants from KINECT 2 and KINECT 3 provided a sufficient sample to assess the effects of valbenazine on TD symptoms in this population. Our findings indicate that once-daily treatment with valbenazine improved TD in adults with a primary mood disorder.

The demographics of these patients (i.e., age, sex, race), along with mean TD duration (approximately 5–6 years) and AIMS total score at baseline (approximately 10–11 points), were generally consistent with overall study populations in recent TD trials of newly approved VMAT2 inhibitors (Anderson et al., 2017; Factor et al., 2017; Fernandez et al., 2017; Hauser et al., 2017; O'Brien et al., 2015). To move beyond

**Table 2**
Treatment-emergent adverse events during double-blind, placebo-controlled treatment.

| TEAE, *n* (%) | Placebo (*n* = 44) | Valbenazine 40 mg/day (*n* = 28) | Valbenazine 80 mg/day (*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 |

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

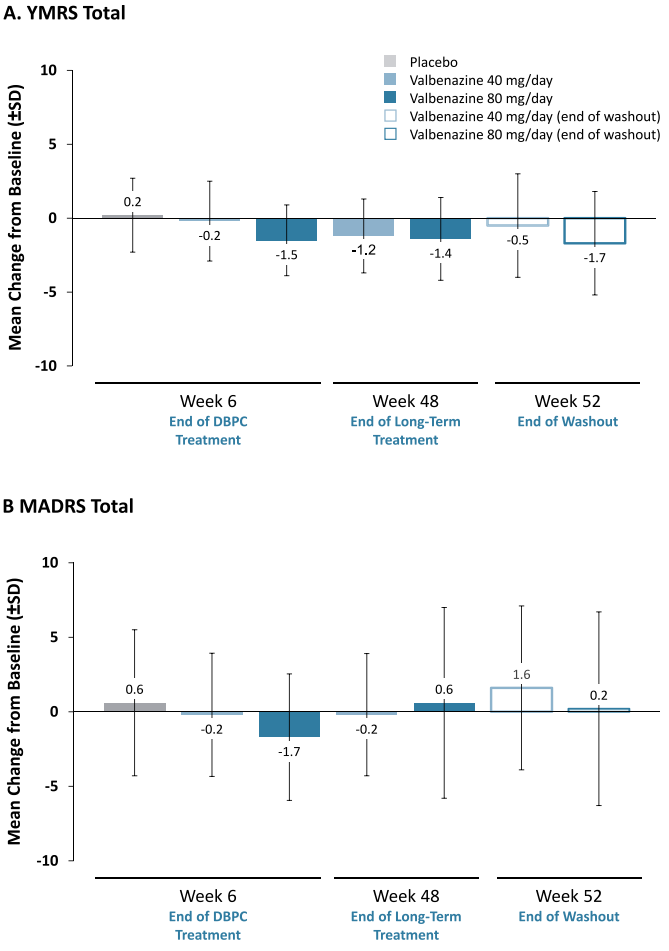


**Fig. 4.** YMRS and MADRS mean score changes from baseline. In participants who received ≥1 dose of study drug and had an available assessment at the study visit. DBPC, double-blind placebo-controlled; MADRS, Montgomery–Åsberg Depression Rating Scale; SD, standard deviation; YMRS, Young Mania Rating Scale.

baseline characteristics typically reported in TD clinical trials, additional analyses were conducted to identify the medical histories of participants with bipolar disorder or depression/major depression. In both diagnosis subgroups, >40% of participants had a history of

gastrointestinal disorders, metabolism/nutritional disorders, musculoskeletal/connective tissue disorders, psychiatric disorders, and vascular disorders.

These medical histories suggest that many of the KINECT 2/KINECT 3 mood patients required some level of ongoing pharmacologic management, which is consistent with their medication history. For example, 41.6% of participants with bipolar disorder or depression/major depression had a history of anxiolytic use, which accords with the 33.6% who reported a history of anxiety-related symptoms. As expected, overall antipsychotic use during the study was more common in bipolar disorder (78.6%) than depression/major depression (62.8%). However, aripiprazole use was more common in depression/major depression (23.3%) than bipolar disorder (14.3%), in keeping with the FDA-approved indication for aripiprazole in MDD. Anticholinergics were permitted in the valbenazine studies; the current analysis indicates that anticholinergics were prescribed more commonly in participants with bipolar disorder (27.1%) than in those with depression/major depression (11.6%). Based on available data, it is not possible to extrapolate the reasons for this difference, and it is conceivable that patients with bipolar disorder happened to have more medical conditions that required anticholinergic treatment. However, one might also speculate that clinicians were more willing to try anticholinergics as a TD treatment in patients with bipolar disorder than in patients with depression/major depression. Another possibility is that the higher lifetime exposure to antipsychotics in patients with bipolar disorder places them at greater risk for disparate extrapyramidal syndromes, for which anticholinergics may have been prescribed despite the known risk of exacerbating TD symptoms.

Results from the exploratory subgroup analyses showed greater mean improvements in AIMS total score with valbenazine (40 and/or 80 mg/day) versus placebo in mood participants categorized by age, sex, BMI, and history of substance abuse. Concomitant use of antipsychotics, antidepressants, anticholinergics, or benzodiazepines did not appear to have a negative impact on AIMS improvement in valbenazine-treated patients.

Although the mean change from baseline in AIMS total score is useful for understanding the overall effect of valbenazine in this group of mood disorder patients, response analyses offer a more granular approach that is based on the number of individual patients who met different thresholds of improvement. At Week 6, a higher percentage of valbenazine-treated participants achieved an AIMS response ($\geq$50% total score improvement from baseline) or CGI-TD response (clinician rating of “much improved” or “very much improved”) as compared to placebo-treated participants. For AIMS and CGI-TD response, an OR $\geq$3 and NNT $\leq$6 was found with both doses of valbenazine. No statistically significant effects of valbenazine on PGIC response were found at Week 6. After long-term treatment, however, the percentage of participants with PGIC response was consistent with CGI-TD response. In all 3 response analyses, some participants maintained clinically meaningful improvements after 4 weeks of washout. However, without larger samples sizes and more detailed analyses, it is difficult to ascertain why some patients continued to experience substantial TD improvements after valbenazine was stopped. More research is needed to assess whether TD is reversible in certain types of patients.

Taken together, the efficacy analyses in this report indicate that patients with a mood disorder had clinically meaningful TD improvements with valbenazine. However, differences in methodology should be noted when interpreting the results. The AIMS was the most controlled outcome measure, since scoring was based on consensus between two independent central video raters who were blinded to treatment and study visit (since the sequence of AIMS videos was scrambled). Anchoring criteria for the AIMS were provided to the central video raters to minimize inter-rater variability. However, since these movement disorder specialists were more likely to have higher inter-rater reliability than inexperienced raters (Lane et al., 1985), the anchors were developed to be as specific—but also as simple—as possible. The CGI-TD was conducted by the site investigator who was blinded to treatment but not study visit. Presumably, each investigator used the same approach for all patients at each visit, but inter-rater reliability across study sites cannot be ascertained. Since the PGIC was self-reported by study participants who may have been more aware of their abnormal movements than patients with schizophrenia, this measure probably had the highest degree of inter-rater variability since each patient determined for him/herself what constituted a rating of “much improved” or “very much improved”. All of these measures have clinical value, but each measure also requires consideration of how the scores were derived.

No unexpected TEAEs or other safety outcomes were found in this population of patients with a primary mood disorder. Since maintenance of psychiatric stability is an important clinical concern, the YMRS and MADRS were administered to mood disorder participants to monitor changes in psychiatric status. Mean score changes from baseline to Week 6 (end of double-blind treatment), Week 48 (end of long-term treatment), and Week 52 (end of washout) were minimal and indicated no worsening of psychiatric status in this population. There was no evidence that valbenazine engendered or exacerbated suicidality in this mood disorder population.

Antipsychotic medications have proven to be a valuable treatment option in the management of bipolar disorder, refractory depression, and other mood-related disorders. Many patients with a mood disorder are highly functional and aware of their abnormal movements, which can lead to embarrassment, social isolation, and other forms of distress. Compared to patients who are unaware of their abnormal movements (Daniel et al., 2016), these mood disorder patients may be more vocal about their TD. Nonetheless, regular screening for TD should be conducted in all patients who are exposed to antipsychotics or other DRBAs (e.g., antiemetics). No single screening method or schedule will be appropriate to all clinics and practices. Assessment can vary from a simple visual observation, to a quick screening tool (as employed in the RE-KINECT screening study [NCT03062033]) (Caroff et al., 2018), to a formal AIMS assessment. Moreover, the impact of TD on quality of life and functional ability should be considered as part of a comprehensive clinical approach to treating this disorder (Kane et al., 2018).

## 5. Limitations

The main study limitation is that the pooled analyses were conducted post hoc, although both KINECT 2 and KINECT 3 included a priori efficacy analyses in patients subgrouped by underlying psychiatric diagnosis (i.e., schizophrenia/schizoaffective disorder, mood disorder). It should also be noted that sample size was limited in the exploratory subgroup analyses, with $<$10 participants in some treatment arms. Therefore, any interpretation of the subgroup results should be made with caution. Larger sample sizes and a more rigorous analytic approach (e.g., regression model) would be needed to draw more definitive conclusions about the effects of various baseline characteristics on treatment outcomes. As discussed, each of the efficacy measures utilized in this study has its own limitations and advantages. Finally, this study does not address improvements in functional ability and/or quality of life, which are important considerations in TD patients.

## 6. Conclusions

Results from two double-blind placebo-controlled trials (6 weeks) and one long-term study (48 weeks) showed that once-daily treatment with valbenazine resulted in clinically meaningful TD improvements in patients with bipolar disorder, MDD, or other mood-related disorders. Future research should endeavor to evaluate the risk of TD in patients with mood disorders who are exposed to antipsychotics, particularly those with multiple risk factors for TD, such as women with comorbid medical conditions (e.g., type 2 diabetes) and older patients. In addition, the long-term safety and efficacy of TD treatments in these

populations should be further investigated.

## Author statement

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All authors contributed to the design and interpretation of the post hoc analyses included in this article. All authors reviewed each draft of the manuscript and approved the final draft for submission.

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## Supplementary materials

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