Changes in Abnormal Involuntary Movement Scale (AIMS) Items 8, 9, and 10: Results from the Valbenazine KINECT 4 Study

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ABSTRACT

Background: In contemporary clinical trials of tardive dyskinesia (TD), efficacy focuses on changes in the Abnormal Involuntary Movement Scale (AIMS) total score. This score is derived from the sum of AIMS items 1 to 7, which rate the severity of abnormal movements in different body regions. However, the AIMS also includes questions about the overall severity of abnormal movements (item 8), incapacitation due to abnormal movements (item 9), and patient's awareness of abnormal movements and distress level (item 10). Data for AIMS items 8, 9, and 10 were collected in a long-term study of once-daily valbenazine (VBZ) in adults with TD (KINECT 4;NCT02405091). These data were analyzed to provide more context for understanding the effects of VBZ in patients with TD.

Methods: KINECT 4 included 48 weeks of treatment followed by a 4-week washout period. Key eligibility criteria included: ages 18 to 85 years; DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or mood disorder; neuroleptic-induced TD for ≥3 months prior to screening; stable psychiatric status (Brief Psychiatric Rating Scale score <50); no high risk of active suicidal ideation or behavior. Stable doses of concomitant medications to treat psychiatric and medical disorders were allowed. VBZ dosing was initiated at 40 mg, with escalation to 80 mg at Week 4 based on clinical assessment of TD and tolerability; a reduction back to 40 mg was allowed if 80 mg was not tolerated. VBZ doses were pooled for analysis. For AIMS items 8, 9, and 10, mean changes from baseline (BL) to Weeks 48 and 52 were analyzed descriptively. For AIMS items 8 and 9, which have the same scale for scoring (0=none to 4=severe), the percentage of participants who shifted from a BL score ≥3 (moderate or severe) to score ≤2 (none to mild) was analyzed at Week 48 and Week 52. A shift analysis was not conducted for Item 10 because the scoring represents 2 different patient types: unaware (score=0) and aware with increasing levels of distress (score=1 to 4).

Results: At Week 48 (end of treatment, n=103), mean improvements from BL (±standard error) were observed as follows: item 8, -2.0 (±0.08); item 9, -1.9 (±0.11); item 10, -1.9 (±0.11). At Week 52 (end of 4-week washout, n=103), mean changes from BL were smaller but indicated some maintenance of VBZ effect: item 8, -0.8 (±0.10); item 9, -1.0 (±0.13); item 10, -0.9 (±0.13). Among participants at the Week 48 visit who had a score ≥3 at BL, most shifted to a score <2 after treatment: item 8, 95.9% (94/98); item 9, 98.3% (58/59). Among those at the Week 52 visit who had a score ≥3 at BL, ~40% maintained improvement after washout: item 8, 46.9% (46/98); item 9, 59.3% (35/59).

Conclusion: Analysis of AIMS items 8 and 9 indicated that long-term treatment with once-daily VBZ (40 or 80 mg) improved overall severity of abnormal movements in patients with TD. Patient incapacitation due to abnormal movements was also improved.

INTRODUCTION

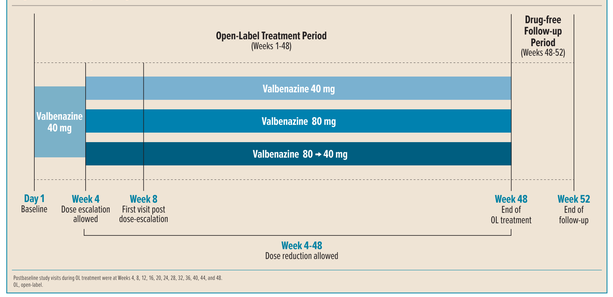
- In contemporary clinical trials of tardive dyskinesia (TD), treatment efficacy has been primarily evaluated based on changes in the Abnormal Involuntary Movement Scale (AIMS) total score[1]
- This total score is the sum of AIMS items 1 to 7, which rate the severity of abnormal movements in different body regions
- In a long-term, open-label study (KINECT 4: NCT02405091), mean changes from baseline in AIMS total score (sum of items 1-7) was analyzed in participants who received once-daily valbenazine at 40 or 80 mg or had a dose reduction from 80 to 40 mg[2]
- KINECT 4 also included AIMS items 8-10, which allow the clinician to assess the overall severity of abnormal movements (item 8), incapacitation due to abnormal movements (item 9), and the patient's awareness of abnormal movements and distress level (item 10)
- Data for these AIMS items were analyzed to provide more context for understanding the effects of valbenazine in patients with TD

METHODS

STUDY DESIGN

- KINECT 4 included a 48-week open-label valbenazine treatment period and a 4-week drug-free period (total of 52 weeks) (**Figure 1**)

Figure 1. Study Design



Postbaseline study visits during OL treatment were at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
OL, open-label.

- All participants received once-daily valbenazine 40 mg for the first 4 weeks
- Participants were escalated to 80 mg at the end of Week 4 if both of the following conditions were met:
  - Clinical Global Impression of Change-Tardive Dyskinesia score of ≥3 ("minimally improved" to "very much worse")
  - Acceptable safety/tolerability with 40 mg, based on investigator judgement
- Participants unable to tolerate 80 mg were allowed a dosage reduction to 40 mg between Week 4 and Week 48; those unable to tolerate 40 mg were discontinued from the study

PARTICIPANTS

- Key inclusion criteria:
  - Adults aged 18 to 85 years with a *Diagnostic and Statistical Manual of Mental Disorders* (e.g., DSM-IV) diagnosis of neuroleptic-induced TD for ≥3 months prior to screening
  - DSM diagnosis of schizophrenia/schizoaffective disorder or mood disorder
  - Moderate or severe TD as qualitatively assessed by an external reviewer
- Key exclusion criteria:
  - Comorbid movement disorder that was more prominent than TD
  - Significant risk for suicidal or violent behavior
- Participants were required to have a stable psychiatric and medical status before entering the study and stable dosages of concomitant medications to treat psychiatric and medical disorders were allowed

STATISTICAL ANALYSES

- Baseline characteristics were analyzed in all participants who received ≥1 dose of valbenazine (safety population)
- All other analyses were conducted in participants who received ≥1 dose of valbenazine and had a relevant postbaseline AIMS assessment; no significance testing was conducted
- AIMS total score was defined as the sum of items 1 to 7, which rate the severity of abnormal movements in different body regions (i.e., face, lips, jaw, tongue, upper extremities, lower extremities, and trunk)
- AIMS item 8 assessed the overall severity of abnormal movements, item 9 assessed incapacitation due to abnormal movements, and item 10 assessed the patient's awareness of abnormal movements and if aware, the level of distress
- Mean changes from baseline to Weeks 48 and 52 were analyzed descriptively for AIMS total score (sum of items 1 to 7) and individual items 8, 9, and 10
- Response and shift analyses were conducted for AIMS items 8 and 9, which have the same scale for scoring (0=none to 4=severe)
  - These analyses were not conducted for item 10 because the scoring represents 2 different patient types: unaware (score=0) and aware with increasing levels of distress (score=1 to 4)
- Two thresholds were used to assess response:
  - Score ≤2 (none to mild) at Week 48 or 52, regardless of baseline score
  - Score ≤1 (none or minimal) at Week 48 or 52, regardless of baseline score
- Two sets of criteria were used to assess shifts:
  - Score ≥3 (moderate or severe) at baseline and score ≤2 at Week 48 or 52
  - Score ≥2 (mild to severe) at baseline and score ≤1 at Week 48 or 52

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RESULTS

- Baseline characteristics and demographics were generally similar across dosage groups (**Table 1**)

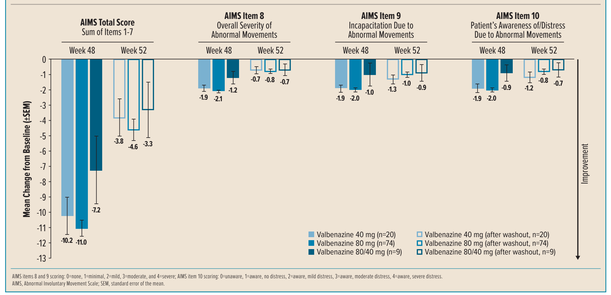
Table 1. Baseline Characteristics (Safety Population)

	Valbenazine 40 mg (n=45)	Valbenazine 80 mg (n=107)	Valbenazine 80/40 mg (n=11)	All Valbenazine (N=163)
Age, mean (SD), years	56.8 (11.2)	57.8 (9.0)	56.3 (8.6)	57.4 (9.6)
Male, n (%)	21 (46.7)	59 (55.1)	6 (54.5)	86 (52.8)
White, n (%)	26 (57.8)	74 (69.2)	10 (90.9)	110 (67.5)
BMI, mean (SD), kg/m²	27.8 (6.0)	29.0 (5.4)	27.5 (3.3)	28.5 (5.5)
BPRS score at screening, mean (SD)	29.2 (6.8)	27.3 (6.6)	28.4 (7.4)	27.9 (6.7)
C-SSRS lifetime suicidal ideation or behavior, n (%)	17 (37.8)	48 (44.9)	4 (36.4)	69 (42.3)
AIMS scores, mean (SD)[a]				
Total score: sum of items 1-7	14.2 (5.5)	15.0 (4.5)	12.8 (4.6)	14.6 (4.8)
Item 8: overall severity of abnormal movements	3.1 (0.5)	3.2 (0.5)	2.7 (0.6)	3.2 (0.5)
Item 9: incapacitation due to abnormal movements	2.4 (0.9)	2.6 (0.8)	2.0 (1.3)	2.5 (0.9)
Item 10: patient's awareness of abnormal movements and distress level	2.8 (0.9)	2.7 (0.7)	2.5 (1.0)	2.7 (0.8)

[a]Score ranges: total (0-28 [none to severe in all 7 body regions]); items 8 and 9 (0-4 [none to severe]); item 10 (0 [no awareness]; 1-4 [aware with no distress to severe distress]).
AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; SD, standard deviation.

- Mean changes from baseline to Week 48 in AIMS total score indicated sustained TD improvements in participants who received once-daily valbenazine at 40 or 80 mg (-10.2 and -11.0, respectively) or had a dose reduction from 80 to 40 mg (-7.2), with some loss of effect at Week 52 (after 4-week washout) (**Figure 2**)
- Mean improvements from baseline to Week 48 (end of treatment) were also found for AIMS items 8 (overall severity of abnormal movements), 9 (incapacitation due to abnormal movements), and 10 (patient's awareness of abnormal movements and distress level), with some loss of effect at Week 52 (after 4-week washout) (**Figure 2**)
  - Mean changes from baseline (±standard error) to Week 48 for all participants (n=103) were as follows: item 8, -2.0 (±0.08); item 9, -1.9 (±0.11); item 10, -1.9 (±0.11)
  - At Week 52 (end of 4-week washout, n=103), mean changes from baseline were smaller but indicated some maintenance of valbenazine effect: item 8, -0.8 (±0.10); item 9, -1.0 (±0.13); item 10, -0.9 (±0.13)

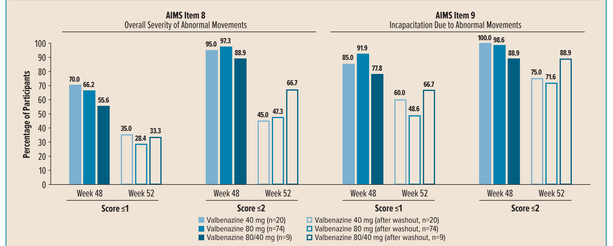
Figure 2. Mean Score Changes from Baseline



AIMS items 8 and 9 scoring: 0=none, 1=minimal, 2=mild, 3=moderate, and 4=severe; AIMS item 10 scoring: 0=unaware, 1=aware, no distress, 2=aware, mild distress, 3=aware, moderate distress, 4=aware, severe distress.
AIMS, Abnormal Involuntary Movement Scale; SEM, standard error of the mean.

- In all valbenazine-treated participants, response rates at Week 48 were >85% for AIMS item 8 (score ≤2) and item 9 (score ≤2), indicating none to mild overall severity and incapacitation due to abnormal movements, respectively; response rates decreased for both items at Week 52 (**Figure 3**)

Figure 3. Participants Meeting Response Thresholds



AIMS, Abnormal Involuntary Movement Scale

- At Week 48, >90% of all participants met one or both sets of shift criteria for AIMS items 8 and 9 (**Table 2**)
  - The percentage of participants meeting shift criteria decreased at Week 52, but some maintained improvement after having discontinued valbenazine for 4 weeks

Table 2. Participants Meeting Shift Criteria

		Valbenazine 40 mg	Valbenazine 80 mg	Valbenazine 80/40 mg	All Valbenazine
Shift from score ≥3 at baseline to score ≤2, n/N (%)					
AIMS item 8	Week 48 Week 52	17/18 (94) 8/18 (44)	71/73 (97) 34/73 (47)	6/7 (86) 4/7 (57)	94/98 (96) 46/98 (47)
AIMS item 9	Week 48 Week 52	10/10 (100) 6/10 (60)	45/46 (98) 27/46 (59)	3/3 (100) 2/3 (67)	58/59 (98) 35/59 (59)
Shift from score ≥2 at baseline to score ≤1, n/N (%)					
AIMS item 8	Week 48 Week 52	14/20 (70) 7/20 (35)	49/74 (66) 21/74 (28)	5/8 (63) 3/8 (38)	68/102 (67) 31/102 (30)
AIMS item 9	Week 48 Week 52	16/18 (89) 11/18 (61)	62/68 (91) 32/68 (47)	6/6 (100) 4/6 (67)	84/92 (91) 47/92 (51)

AIMS, Abnormal Involuntary Movement Scale; N, number of participants with score ≥3 or ≥2 at baseline; n, number of participants who shifted to score ≤2 or ≤1 at Week 48 or 52.

CONCLUSIONS

- Mean changes from baseline in AIMS scores indicated that long-term treatment with once-daily valbenazine (40 or 80 mg) improved TD symptoms in 7 body regions (total score), overall severity of abnormal movements (item 8), incapacitation due to abnormal movements (item 9), and awareness/distress in patients with TD (item 10)
- Response and shift analyses for AIMS items 8 and 9 indicated that a substantial proportion of participants had clinically meaningful improvements in these measures after 48 weeks of valbenazine treatment
- Some patients continued to maintain these improvements after a 4-week washout of valbenazine

REFERENCES

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