Using Item 8 of the Abnormal Involuntary Movement Scale (AIMS) to Assess Improvement in Patients with Tardive Dyskinesia

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INTRODUCTION

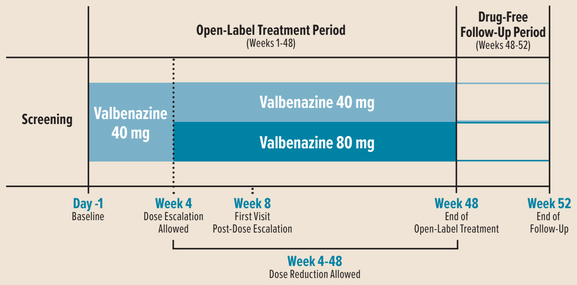
- Tardive dyskinesia (TD), a persistent and potentially disabling movement disorder, can emerge with prolonged exposure to antipsychotics or other dopamine receptor blocking agents[1,2]
- Valbenazine is a highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor approved for the treatment of TD in adults[3]
- Valbenazine was shown to reduce TD symptoms in 3 randomized, double-blind, placebo-controlled trials[4-6] and 3 long-term studies[7-9]
- In contemporary TD studies, the primary efficacy outcome is usually based on changes from baseline in the Abnormal Involuntary Movement Scale (AIMS) total score (sum of AIMS items 1-7)
- However, a low AIMS total score can be ambiguous when presented without context; for example, a total score of 4 could represent any of the following:
  - Rating of 1 (minimal) in 4 different body regions
  - Rating of 2 (mild) in 2 different body regions
  - Rating of 3 (moderate) in 1 region and rating of 1 (minimal) in another region
  - Rating of 4 (severe) in a single region
- Physicians often use (knowingly or unknowingly) informal assessments to gauge TD severity in their patients (e.g., mild, moderate, or severe)
- Therefore, data from a long-term valbenazine study, KINECT 4 (NCT02405091), were analyzed post hoc to evaluate the potential of AIMS item 8 (clinician's global impression of severity) as simple clinical measure that could be used in lieu of the AIMS total score

METHODS

STUDY DESIGN

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

Figure 1. Study Design



Valbenazine treatment started on Day 1.
40 mg group: never had a dose increase to 80 mg.
80 mg group: received 40 mg and increased to 80 mg, with or without dose reduction after Week 4.

- All participants received valbenazine 40 mg for 4 weeks
- Participants could be escalated to 80 mg at the end of Week 4 if both of the following conditions were met:
  - Clinical Global Impression of Change-TD score of ≥3 ("minimally improved" to "very much worse")
  - Acceptable safety/tolerability with 40 mg, based on investigator judgement

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, qualitatively assessed by an external reviewer at screening
  - Stable psychiatric and medical status
- Key exclusion criteria:
  - Comorbid movement disorder that was more prominent than TD
  - Significant risk for suicidal or violent behavior
- Stable doses of concomitant medications to treat the psychiatric and medical conditions were allowed

ANALYSES

- Analyses were based on AIMS item 8 ("severity of abnormal movements overall") using two sets of AIMS item 8 scores (**Table 1**):
  - Protocol-based method: based on investigators' ratings of item 8 using protocol-defined descriptors
  - Post hoc method: based on investigators' highest single score from items 1-7
- Mean AIMS item 8 scores with standard deviation (SD) were analyzed at baseline and by study visit
- Three shift analyses were conducted based on the following criteria:
  - Score 4 at baseline (severe) and score ≤3 at Week 48 (none to moderate)
  - Score ≥3 at baseline (moderate or severe) and score ≤2 at Week 48 (none to mild)
  - Score ≥2 at baseline (mild to severe) and score ≤1 at Week 48 (none or minimal)

Table 1. AIMS Scoring and Descriptors in KINECT 4[a]

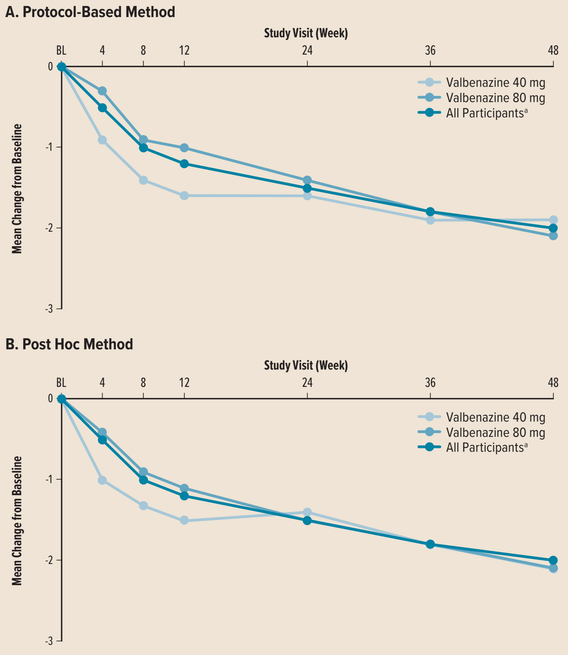
Score	Protocol-Defined Descriptors
0	**No dyskinesia**
1	**Minimal or slight dyskinesia:** Low amplitude, present during some but not most of exam
2	**Mild dyskinesia:** Low amplitude and present during most of exam (or moderate amplitude and present during some of exam)
3	**Moderate dyskinesia:** Moderate amplitude and present during most of exam
4	**Severe dyskinesia:** Maximal amplitude and present during most of exam

[a]For AIMS items 1-7.
No other specific or additional direction was provided for AIMS item 8; scores were based on each investigator's individual judgement. When used clinically, a common practice is to score AIMS item 8 using the highest single score from items 1-7.[10]

RESULTS

- In general, results were similar between the protocol-based scoring and the post hoc-based scoring methods
- In all participants (N=163), mean scores for AIMS item 8 and changes from baseline (±SD) were as follows:
  - At baseline: protocol, 3.2 ± 0.6; post hoc, 3.3 ± 0.6 (moderate-to-severe)
  - At Week 48: protocol, 1.2 ± 0.7; post hoc, 1.4 ± 0.7 (minimal-to-mild)
  - Mean change from baseline to Week 48: protocol, -2.0 ± 0.8; post hoc, -2.0 ± 0.9 (**Figure 2**)

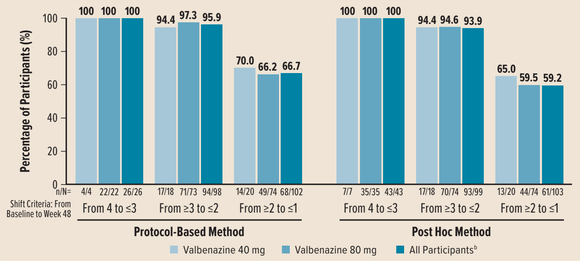
Figure 2. AIMS Mean Change from Baseline by Visit



[a]Includes 11 participants who had a dose reduction from 80 to 40 mg after Week 4.
AIMS, Abnormal Involuntary Movement Scale; BL, baseline.

- Results from AIMS item 8 shift analyses were similar between the scoring methods (**Figure 3**)
  - In participants with a score of 4 at baseline (severe), 100% shifted to a score ≤3 at Week 48 (none to moderate)
  - In participants with a score ≥3 at baseline (moderate or severe), >90% shifted to a score ≤2 at Week 48 (none to mild)
  - In participants with a score ≥2 at baseline (mild to severe), >50% shifted to a score ≤1 at Week 48 (none or minimal)

Figure 3. Participants Meeting Shift Criteria[a]



[a]Based on participants who had available AIMS assessments at baseline and Week 48.
[b]Includes 9 participants who had a dose reduction from 80 to 40 mg after Week 4.

CONCLUSIONS

- Once-daily valbenazine treatment resulted in improved AIMS item 8 scores (clinician's global impression of severity) in patients with TD
- Shift analyses indicated that most participants had a clinically meaningful improvement at Week 48 (end of treatment)
- Similar results were found whether AIMS item 8 scores were based on report by site raters (protocol-based method) or the highest items 1-7 scores (post hoc method)
- These results demonstrate that AIMS item 8 scores may be an appropriate clinical measure for assessing changes in TD severity
- Moreover, the convention of scoring AIMS item 8 based on the highest single score from AIMS items 1-7 is simple to communicate and can yield clinically useful and actionable data; this approach avoids the need to interpret the AIMS total score (sum of AIMS items 1-7), which can be ambiguous when viewed in isolation

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