Effects of Once-Daily Valbenazine on Tardive Dyskinesia by Body Region: Shift Analyses of KINECT 3 Study Data

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INTRODUCTION

- Tardive dyskinesia (TD), a potentially irreversible movement disorder associated with exposure to dopamine receptor blocking agents (DRBAs) such as antipsychotics, is characterized by involuntary choreic or athetoid movements in 1 or more body regions[1,2]
- The Abnormal Involuntary Movement Scale (AIMS) is used to detect and monitor changes in dyskinesia severity over time
- The first 7 items of the AIMS evaluate dyskinesia severity in different body regions (face, lips, jaw, tongue, upper extremities, lower extremities, trunk)
- An AIMS total score can be calculated by summing the scores for items 1-7, each of which is scored from 0 (none) to 4 (severe)
- Because the AIMS total score is not a linear scale, it may not fully represent the clinical severity of TD
- For example, a moderate or severe rating in a single body region would result in a "low" AIMS total score of 3 or 4, but this level of dyskinesia could still be very troubling to the patient
- Because patients may experience abnormal movements in different regions, analyses are needed that focus on individual AIMS items in addition to AIMS total score
- In clinical trials of valbenazine (INGREZZA), the first and only FDA-approved medication for the treatment of adults with TD, mean improvements in AIMS total score were significantly greater with valbenazine as compared with placebo[3,4]
- Analyses of AIMS item data from the KINECT 3 trial were conducted to provide more specific information about the effects of valbenazine on TD in different body regions

OBJECTIVES

- To explore TD improvements across body regions using AIMS item scores and to show clinically meaningful changes in these regions using category shifts (i.e., improvement in individual AIMS items from moderate or severe at baseline to mild or better after treatment)

METHODS

STUDY DESIGN

- KINECT 3 was a 6-week, randomized, double-blind, placebo-controlled (DBPC) study of valbenazine in adults with a diagnosis of schizophrenia/schizoaffective disorder or mood disorder and TD
  - Concomitant use of stable doses of antipsychotics was permitted during the trial
  - Participants were randomized 1:1:1 to once-daily valbenazine 40 mg, 80 mg, or placebo

ANALYSES

- Analyses were based on items 1-7 of the AIMS (**Table 1**), with each item scored on a 0 to 4 scale as follows:
  - 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 the exam)
  - 3=moderate dyskinesia: moderate amplitude and present during most of exam
  - 4=severe dyskinesia: maximal amplitude and present during most of the exam

Table 1: Abnormal Involuntary Movement Scale[a]

AIMS Item	Description	Score
1	**Muscles of facial expression** e.g., movements of forehead, eyebrows, periorbital area, cheeks; includes frowning, blinking, smiling, grimacing	0-4
2	**Lips and perioral area** e.g., puckering, pouting, smacking	0-4
3	**Jaw** e.g., biting, clenching, chewing, mouth opening, lateral movement	0-4
4	**Tongue** e.g., increase in movement both in and out of mouth, not inability to sustain movement	0-4
5	**Upper extremities (arms, wrists, hands, fingers)** e.g., movements that are choreic (rapid, objectively purposeless, irregular, spontaneous) or athetoid (slow, irregular, complex, serpentine); does not include tremor (repetitive, regular, rhythmic movements)	0-4
6	**Lower extremities (legs, knees, ankles, toes)** e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0-4
7	**Trunk (neck, shoulders, hips)** e.g., rocking, twisting, squirming, pelvic gyrations; includes diaphragmatic movements	0-4

[a]Adapted from Guy 1976[5]

- Mean scores for AIMS items 1-7 were analyzed at baseline and Week 6 in the intent-to-treat (ITT) population, defined as participants with a baseline and at least 1 postbaseline AIMS dyskinesia total score assessment in the DBPC period
- Category shifts for AIMS items 1-7 were analyzed post hoc and defined as an improvement from score ≥3 at baseline (moderate/severe rating) to score ≤2 (mild/minimal/none rating) at Week 6
- Mean score improvements and category shifts were analyzed descriptively in participants who had an available AIMS assessment at baseline and Week 6

RESULTS

- Baseline demographics and disease characteristics were generally similar across treatment groups (**Table 2**)

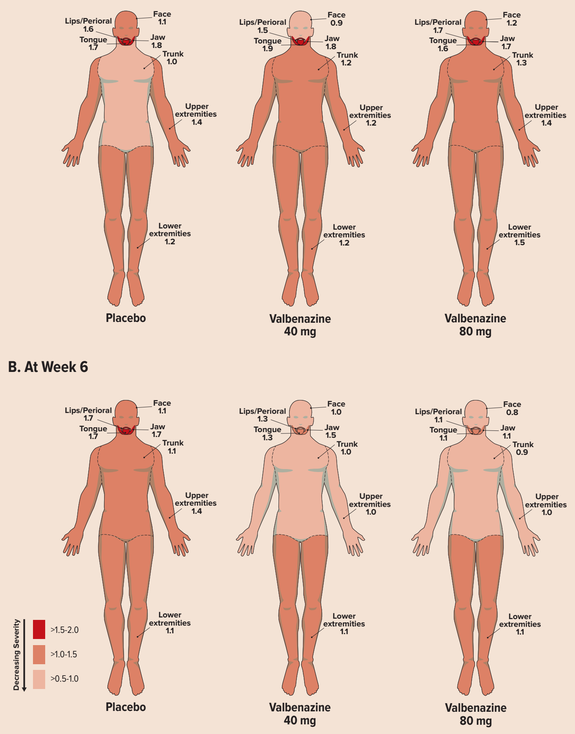
Table 2. Baseline Demographics and Disease Characteristics (ITT Population)

	Placebo (n=76)	Valbenazine 40 mg (n=70)	Valbenazine 80 mg (n=79)
Age, mean years (SD)	57.0 (10.5)	55.3 (8.6)	56.0 (10.1)
Male, n (%)	42 (55.3)	40 (57.1)	39 (49.4)
White, n (%)	43 (56.6)	41 (58.6)	44 (55.7)
Schizophrenia/schizoaffective disorder, n (%)	50 (65.8)	46 (65.7)	52 (65.8)
Mood disorder, n (%)	26 (34.2)	24 (34.3)	27 (34.2)

ITT, intent-to-treat; SD, standard deviation.

- At baseline, mean scores were in the range of >1.0 to 2.0 (minimal to mild) for most AIMS items in all treatment groups; however, scores ≤1 (none to minimal) were observed for the trunk in the placebo group and the face in the valbenazine 40 mg group (**Figure 1A**)
- At Week 6, mean AIMS item scores ≤1 (none to minimal) were observed for the face, upper extremities, and trunk in both valbenazine treatment groups; no region in the placebo treatment group had a mean AIMS item score ≤1 (**Figure 1B**)
- From baseline to Week 6, regions with ≥25% mean improvement in the AIMS item score were as follows:
  - Placebo: no region
  - Valbenazine 40 mg: tongue (32%)
  - Valbenazine 80 mg: lips/perioral (35%), jaw (35%), face (33%), tongue (31%), trunk (31%), upper extremities (29%), lower extremities (27%)
- From baseline to Week 6, small increases in mean AIMS item score were observed for lips/perioral and trunk in the placebo group and for face in the valbenazine 40 mg group (mean score change of +0.1 for each of these regions)

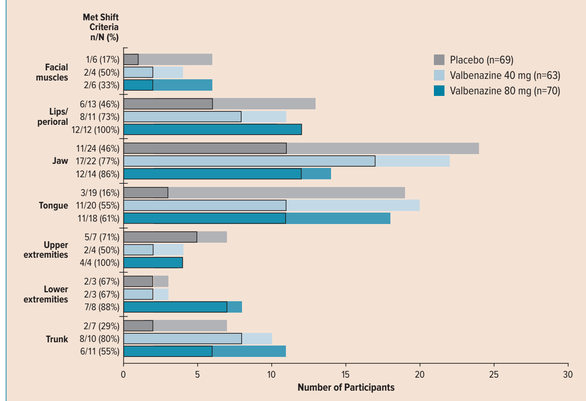
Figure 1. Mean AIMS Item Scores at Baseline and Week 6 (ITT Population)



No AIMS item had a mean score ≤0.5 or >2.0 at baseline or Week 6.
AIMS, Abnormal Involuntary Movement Scale; ITT, intent-to-treat.

- Among participants in the ITT population with an available AIMS assessment at Week 6 (80 mg, n=70; 40 mg, n=63; placebo, n=69), more participants met the shift criteria with valbenazine (both doses) vs. placebo in all AIMS items except for upper extremities (**Figure 2**)
- The number of participants in any treatment group with at least 1 baseline AIMS item score ≥3 was as follows: face (n=16), lips/perioral (n=36), jaw (n=60), tongue (n=57), upper extremities (n=15), lower extremities (n=14), trunk (n=28)
- Within the subgroup of participants with at least 1 baseline AIMS item score ≥3, more participants met the shift criteria for AIMS items (i.e., baseline score ≥3 and Week 6 score ≤2) with valbenazine (both doses) vs. placebo (**Figure 2**); AIMS items that had >50% of participants who met shift criteria were as follows:
  - Placebo: upper extremities (71%), lower extremities (67%)
  - Valbenazine 40 mg: trunk (80%), jaw (77%), lips/perioral (73%), lower extremities (67%), tongue (55%), facial muscles (50%), upper extremities (50%)
  - Valbenazine 80 mg: lips/perioral (100%), upper extremities (100%), lower extremities (88%), jaw (86%), tongue (61%), trunk (55%)
- The percentage of participants who met shift criteria in ≥2 body regions was greater with valbenazine 80 mg (18.6%) and valbenazine 40 mg (22.2%) vs. placebo (8.7%)

Figure 2. Participants Meeting AIMS Shift Criteria



Each full bar represents the number of participants with an item score ≥3 at baseline. Darker tone with outline indicates participants who met shift criteria at Week 6; lighter tone indicates participants who did not meet shift criteria.
n, number of subjects who met shift criteria; N, number of subjects with baseline item scores ≥3.

CONCLUSIONS

- Mean score changes for AIMS items 1-7 indicated a greater magnitude of TD improvement across all body regions with valbenazine relative to placebo
- In the overall population, the percentage of participants with a categorical shift (i.e, AIMS item score of ≥3 at baseline and score ≤2 at Week 6) was higher in both valbenazine dose groups than in the placebo group for 6 of 7 AIMS items
- These exploratory analyses suggest that clinically meaningful improvements occurred more frequently with valbenazine than with placebo in the KINECT 3 study

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Disclosures: This study was supported by Neurocrine Biosciences, Inc. C. Verghese does not report any conflicts of interest. R. McIntyre has been an advisory board member of Bristol-Myers Squibb, Eli Lilly, Forest, Lundbeck, Merck, Otsuka, Pfizer, Shire, Sunovion, and Takeda; received speakers' fees from Astra-Zeneca, Eli Lilly, Forest, Janssen-Ortho, Lundbeck, Merck, Pfizer, Otsuka, Sunovion, and Takeda; and received research grants from Astra-Zeneca, BMS, Eli Lilly, Forest, Janssen-Ortho, Lundbeck, Pfizer, Shire, and Sunovion. J. Burke, H. Le, C. Wright and G. Liang are employees of Neurocrine Biosciences, Inc. Writing assistance was provided by Prescott Medical Communications Group, Inc., Chicago, IL.

POSTER PRESENTED AT THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY
MAY 29-JUNE 2, 2017; MIAMI, FL