An MCID for AIMS Dyskinesia Total Score Change in Subjects with Tardive Dyskinesia

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INTRODUCTION

- Tardive dyskinesia (TD) is a persistent movement disorder associated with prolonged exposure to a dopamine receptor blocking agent (DRBA), such as an antipsychotic[1]
- Valbenazine (INGREZZA™) is the first and only medication approved for the treatment of TD in adults
- In recent double-blind, placebo-controlled (DBPC) trials of valbenazine,[2,3] efficacy was demonstrated using the Abnormal Involuntary Movement Scale (AIMS) dyskinesia total score, defined as the sum of items 1-7
- AIMS scoring was based on consensus of 2 central AIMS video raters who were blinded to treatment group and sequence of visits
- The minimal clinically important difference (MCID) can be defined as the magnitude of score change in subjects who experienced a defined level of clinical benefit[4]
- No MCID has yet been determined for the AIMS total score in patients with TD

OBJECTIVE

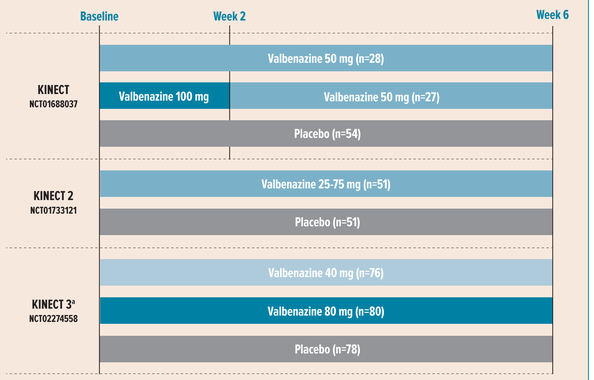
- To establish a potential MCID for the AIMS total score in TD using an anchor-based approach and data from DBPC trials of valbenazine

METHODS

STUDY DESIGN

- Data were pooled from three 6-week, randomized, double-blind, placebo-controlled trials of once-daily valbenazine in adults with TD (**Figure 1**)
  - The pooled valbenazine 80 mg group included participants from the 80 mg group in KINECT 3 and the 75 mg group in KINECT 2
  - The pooled valbenazine 40 mg group included participants from the 40 mg group in KINECT 3, as well as the 50 mg groups in KINECT (including participants who initially received 2 weeks of valbenazine 100 mg) and KINECT 2
  - Participants who received valbenazine 25 mg in KINECT 2 (i.e., no dose escalation to 50 or 75 mg) were excluded from analyses

Figure 1. Study Design



[a]KINECT 3 80 mg group received 40 mg for the first week.
n-values indicate the number of participants who were randomized to treatment.

PARTICIPANTS

- Key inclusion criteria:
  - *Diagnostic and Statistical Manual of Mental Disorders* (e.g., DSM-IV) diagnosis of schizophrenia, schizoaffective disorder, or mood disorder; required to be psychiatrically stable prior to study entry (e.g., Brief Psychiatric Rating Scale score <50 at screening)
  - DSM diagnosis of DRBA-induced TD for ≥3 months prior to screening
  - Moderate or severe TD as qualitatively assessed by a blinded, external reviewer using an AIMS video conducted at screening
- Key exclusion criteria:
  - Active, clinically significant, and unstable medical condition within 1 month prior to screening
  - Comorbid movement disorder that was more prominent than TD
  - Significant risk for active suicidal ideation, suicidal behavior, or violent behavior
- Stable doses of concomitant medications (including antipsychotics) to treat psychiatric disorders were allowed throughout the studies

ANALYSES

- Measures used to evaluate TD improvement included:
  - Mean change from baseline to Week 6 in the AIMS total score
  - Mean score at Week 6 for the Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD)
- The MCID analyses were conducted in a pooled intent-to-treat (ITT) population, defined as participants from the individual studies who received ≥1 dose of study drug and had ≥1 post-baseline AIMS assessment
- Two definitions of CGI-TD response were used as anchors for the MCID analyses:
  - Robust response: CGI-TD score of 1 ("very much improved") or 2 ("much improved") at Week 6
  - Minimal response: CGI-TD score of 3 ("minimally improved") or better
- Based on these anchors, two potential MCIDs were determined as follows:
  - AIMS mean/median score change from baseline to Week 6 in all participants with a robust CGI-TD response
  - AIMS mean/median score change from baseline to Week 6 in all participants with a minimal CGI-TD response
  - Both MCID analyses were conducted regardless of treatment
- Since fluctuations in TD severity should be considered when interpreting an MCID, a cumulative distribution function (CDF) analysis was performed to assess the variability of AIMS mean score changes in each pooled treatment group

RESULTS

- Baseline characteristics were similar across treatment groups in the pooled ITT population (**Table 1**)

Table 1. Baseline Characteristics (Pooled ITT Population)

	Placebo (n=158)	Valbenazine 40 mg (n=114)	Valbenazine 80 mg (n=101)
Age, mean years (SD)	55.8 (10.1)	54.9 (9.1)	56.2 (10.4)
Male, n (%)	89 (56.3)	72 (63.2)	55 (54.5)
Race, n (%)			
White	86 (54.4)	64 (56.1)	62 (61.4)
Black	63 (39.9)	44 (38.6)	36 (35.6)
Psychiatric diagnosis group, n (%)			
Schizophrenia/schizoaffective disorder	116 (73.4)	90 (78.9)	61 (60.4)
Mood disorder	42 (26.6)	24 (21.1)	40 (39.6)
Concomitant use of antipsychotics, n (%)			
Any antipsychotic	130 (82.3)	102 (89.5)	77 (76.2)
Atypical only	102 (78.5)	77 (75.5)	63 (81.8)
Typical only or both	28 (21.5)	25 (24.5)	14 (18.2)
BPRS score at screening, mean (SD)	30.5 (7.6)	31.6 (7.9)	28.9 (6.8)
AIMS score, mean (SD)	8.9 (4.4)	9.0 (4.2)	9.5 (3.6)

AIMS, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale; ITT, intent-to-treat; SD, standard deviation.

- Mean improvements in AIMS total score were greater with valbenazine relative to placebo at Week 6 (**Table 2**)
- Mean CGI-TD scores were also favorable with valbenazine relative to placebo
- 95% confidence intervals (CIs) for mean differences between valbenazine (40 mg, 80 mg) and placebo did not cross 1, indicating statistical significance for both the AIMS and CGI-TD results

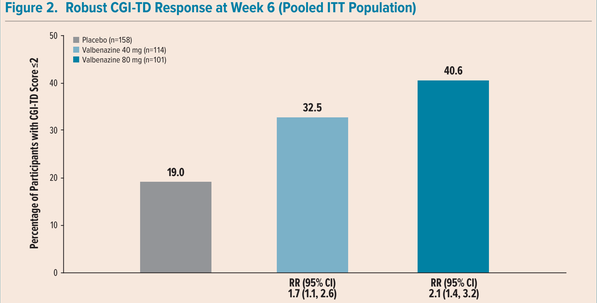
Table 2. Effects of Valbenazine on Tardive Dyskinesia at Week 6

	Placebo (n=158)	Valbenazine 40 mg (n=114)	Valbenazine 80 mg (n=101)
AIMS total score[a]			
LS mean change from baseline (SE)	-0.7 (0.27)	-2.4 (0.33)	-3.2 (0.36)
Mean difference (95% CI)	--	-1.7 (-2.5, -0.9)	-2.6 (-3.4, -1.7)
CGI-TD score[b]			
LS mean (SE)	3.1 (0.07)	2.8 (0.09)	2.7 (0.09)
Mean difference (95% CI)	--	-0.3 (-0.5, -0.1)	-0.4 (-0.6, -0.2)

[a]Analyzed using an analysis of covariance model with valbenazine dose group, study, and psychiatric diagnosis group as fixed effects, and baseline AIMS total score as a covariate.
[b]Analyzed using an analysis of variance model with valbenazine dose group, study, and psychiatric diagnosis group.
AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; CI, confidence interval; LS, least squares; SE, standard error.

- At Week 6, the percentage of participants with a robust CGI-TD response (i.e., rating of "very much improved" or "much improved") was higher in both valbenazine dose groups than in the placebo group (**Figure 2**)
  - Relative risk for valbenazine 40 mg and 80 mg vs placebo were 1.7 and 2.1, respectively
  - The lower 95% CIs in both valbenazine dose groups was >1, indicating statistical significance

Figure 2. Robust CGI-TD Response at Week 6 (Pooled ITT Population)



CI, confidence interval; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; ITT, intent-to-treat; RR, relative risk vs placebo.

- In all participants with a robust CGI-TD response, regardless of treatment, the median change from baseline in AIMS total score was -3.0 (**Table 3**)
  - In participants with a minimal response (i.e., rating of "minimally improved" or better), the median change from baseline was -2.0
  - These median score changes may be considered potential MCIDs for the AIMS total score in adults with TD

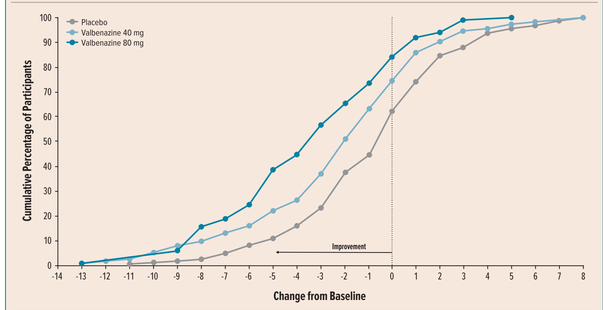
Table 3. AIMS Score Change from Baseline at Week 6 by CGI-TD Response Category (Pooled ITT Population)

AIMS Total Score	Robust: CGI-TD Score ≤2[a] (N=108)	Minimal: CGI-TD Score ≤3[b] (N=269)
Mean	-3.4	-2.2
Standard deviation	4.0	3.8
Standard error	0.39	0.23
Median	-3.0	-2.0
Minimum, maximum	-13, 8	-13, 8

[a]Rating of "much improved" or better at Week 6.
[b]Rating of "minimally improved" or better at Week 6.
AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; ITT, intent-to-treat.

- Consistent with mean changes from baseline in AIMS total score (**Table 2**), CDF curves for the valbenazine groups were shifted left from placebo group in a dose-related manner (**Figure 3**)
  - These shifts indicated that the magnitude of improvement in placebo-treated participants was less than the improvement seen in valbenazine-treated participants
  - CDF analyses also indicated that most placebo-treated participants had an AIMS score change of -4 to +4, which may represent the natural variability of TD severity
  - This range was consistent with the baseline mean AIMS total score standard deviation of 4.4 in the placebo group (**Table 1**)

Figure 3. CDF of AIMS Total Score Change from Baseline to Week 6 (Pooled ITT Population)



AIMS, Abnormal Involuntary Movement Scale; CDF, cumulative distribution function; ITT, intent-to-treat.

CONCLUSIONS

- Data pooled from 3 DBPC trials showed improvements in TD severity with valbenazine, as indicated by mean changes from baseline in the AIMS total score and CGI-TD mean scores after 6 weeks of treatment
- In participants who achieved a minimal CGI-TD response (i.e., score ≤3 at Week 6), the median AIMS total score change was -2.0
- In all participants who achieved a robust CGI-TD response (i.e., score ≤2 at Week 6), the median AIMS total score change was -3.0, which is consistent with the placebo-corrected AIMS mean score change of -3.1 found with once-daily valbenazine 80 mg in the KINECT 3 Phase 3 trial[3]
- In these studies, the relative risk of a robust CGI-TD response was 1.7 times greater with valbenazine 40 mg vs placebo, and 2.1 times greater with valbenazine 80 mg vs placebo
- These 2- and 3-point thresholds may be used as MCID for AIMS total score change in patients with TD in trials using similar methodology
- Additional analyses are warranted for broader generalizability of MCID for AIMS total score changes

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