Effects of Valbenazine on Emotional Health and Psychiatric Stability in Adults With Huntington's Disease

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ABSTRACT DESCRIPTION

In KINECT®-HD, adults with Huntington's disease (HD)-associated chorea received once-daily valbenazine or placebo for 12 weeks. As measured by the patient-reported Huntington's Disease Health Index (HD-HI), some aspects of emotional health improved with valbenazine among participants affected at baseline. No worsening in psychiatric symptoms or suicidality was observed with valbenazine.

INTRODUCTION

- Individuals with HD have a mutation in the *HTT* gene that causes neurodegeneration and leads to abnormal movements (e.g., chorea), psychiatric symptoms (e.g., apathy, depression, irritability, aggression, anxiety), and cognitive decline[1-4]
- Valbenazine, a highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor, is approved for once-daily treatment of chorea in adults with HD and for tardive dyskinesia[5]
- In a 12-week, phase 3 clinical trial (KINECT-HD: NCT04102579), valbenazine significantly improved HD-associated chorea versus placebo, as assessed using the Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) score[6]
- KINECT-HD also implemented the HD-HI, a validated, disease-specific, patient-reported outcome that measures burden due to HD[7]
- The emotional health subscale of the HD-HI included items related to feelings of anxiety, anger, and frustration, along with disease-related fears and changes in mood
- To explore the effects of valbenazine on emotional health, post-hoc analyses of the HD-HI emotional health subscale items were conducted
- Results of these analyses, along with psychiatric-related safety outcomes, are presented

OBJECTIVES

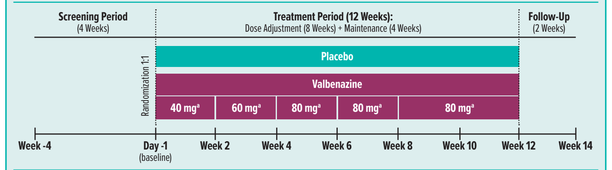
- Understand that for affected individuals, aspects of emotional health may improve with valbenazine
- Recognize that in the 12-week KINECT-HD study, psychiatric symptoms remained stable, and no worsening in suicidal ideation was observed with valbenazine
- Acknowledge that changes in psychiatric symptoms and emergence of suicidal thinking or behavior should be regularly monitored in patients receiving medication for chorea

METHODS

STUDY DESIGN

- Study participants were randomized (1:1) to once-daily valbenazine or placebo for 12 weeks (**Figure 1**)
  - Valbenazine was initiated at 40 mg and increased in 20-mg increments at the end of weeks 2, 4, or 6 to a target dose of 80 mg
  - Doses could be reduced at any time during the dose-adjustment period if not tolerated, with multiple dose reductions allowed; the lowest allowed dose was 20 mg
  - During the maintenance period, the dose could be reduced once if not tolerated, but further escalation was prohibited

Figure 1. KINECT-HD Study Design



[a]Doses represent the maximum daily doses during each treatment period.

PARTICIPANTS

- Key inclusion criteria:
  - Adults aged 18 to 75 years with a diagnosis of motor manifest HD with an expanded CAG repeat (≥37) in the *HTT* gene prior to study entry
  - UHDRS TMC score ≥8 at screening and baseline
  - UHDRS Total Functional Capacity score ≥5 at screening, with score of 5–10 requiring presence of a reliable caregiver to ensure study drug administration and study visit attendance
- Key exclusion criteria:
  - Unstable, untreated, or undertreated psychiatric illness
  - Score ≥11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS)
  - Any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) per the Columbia-Suicide Severity Rating Scale (C-SSRS) in the 3 months prior to screening or baseline
  - Use of antipsychotics or other dopamine receptor blockers, strong CYP3A4 inducers, dopamine agonists/precursors, monoamine oxidase inhibitors, or VMAT2 inhibitors; however, stable doses of antidepressant therapy for ≥8 weeks prior to baseline were allowed in individuals with history of depression

EMOTIONAL HEALTH AND PSYCHIATRIC STABILITY ANALYSES

- Items comprising the HD-HI emotional health subscale were analyzed post hoc in participants who reported being "affected" to any degree by these items
  - For each item, "affected" participants were defined as individuals who had a baseline item score ≥2 ("it affects my life a little" or worse)
  - Observed values and mean changes from baseline to week 10 and week 12 were analyzed by treatment group using an analysis of covariance (ANCOVA) model
- Psychiatric stability was monitored in all participants receiving ≥1 dose of study drug and reported by the following:
  - Incidence of psychiatric-related treatment-emergent adverse events (TEAEs)
  - Shifts from baseline to maximum post-baseline value in the C-SSRS
  - Mean changes from baseline to week 12 in HADS anxiety and depression scales
- Outcomes were analyzed descriptively

RESULTS

- Demographics and baseline characteristics in the full analysis set (N=125) are presented (**Table 1**)
  - Baseline HD-HI emotional health scores were slightly lower (better) in the valbenazine group compared to the placebo group

Table 1. Demographics and Baseline Characteristics (Full Analysis Set)

	Placebo (n=61)	Valbenazine (n=64)
Demographics		
Age, mean (SD), years	53.3 (11.4)	54.1 (10.1)
Female, n (%)	35 (57.4)	33 (51.6)
White, n (%)[a]	60 (98.4)	60 (93.8)
Hispanic or Latino, n (%)	3 (4.9)	5 (7.8)
Body mass index, mean (SD), kg/m^2	27.4 (5.7)	26.6 (5.6)
Baseline characteristics		
CAG repeat length, mean (SD)	43.3 (3.1)	43.5 (3.3)
TMC score, mean (SD)[b]	12.1 (2.8)	12.2 (2.3)
HD-HI emotional health score, mean (SD)[c]	21.2 (20.7)	16.6 (18.3)
HADS anxiety score, mean (SD)[d]	5.4 (4.2)	4.0 (4.0)
HADS depression score, mean (SD)[d]	3.6 (3.3)	3.0 (2.6)

[a]Additional self-reported races were as follows: Black/African American (n=1), Asian (n=1), other/unspecified (n=3).
[b]For screening and baseline period (average of each participant's screening and baseline values), per assessment by study investigator. Score range: 0 to 28, with higher scores indicating more severe chorea.
[c]Score range: 0 (no disease burden), 100 (highest disease burden).
[d]Score range: 0-7 (normal), 8-10 (mild), 11-14 (moderate), 15-21 (severe).
HADS, Hospital Anxiety and Depression Scale; HD-HI, Huntington's Disease Health Index; SD, standard deviation; TMC, Total Maximal Chorea.

POST-HOC ANALYSES

- The number of "affected" participants for each HD-HI emotional health item (i.e., those with a baseline rating of "it affects my life a little" or worse) are shown in **Table 2**, along with the mean HD-HI scores at baseline for these affected participants

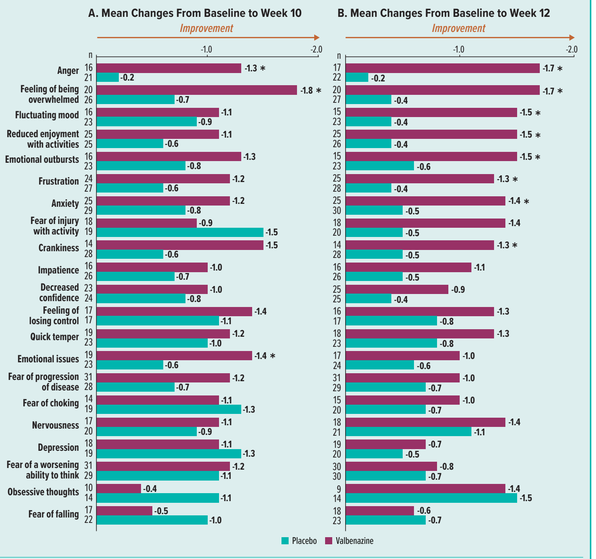
Table 2. Mean Baseline Scores for HD-HI Emotional Health Subscale Items (Affected Participants[a])

	Placebo		Valbenazine	
Emotional Health Item	n	Mean (SD)[b]	n	Mean (SD)[b]
Anger	25	2.6 (0.8)	21	2.7 (0.8)
Feeling of being overwhelmed	31	2.6 (0.9)	23	3.2 (1.0)
Fluctuating mood	27	2.6 (0.7)	16	2.7 (1.0)
Reduced enjoyment with activities	30	2.5 (0.7)	28	2.7 (0.8)
Emotional outbursts	26	2.6 (0.9)	17	2.7 (0.9)
Frustration	32	2.8 (0.8)	29	2.9 (1.1)
Anxiety	32	2.7 (0.9)	30	2.9 (0.9)
Fear of injury with activity	22	2.8 (1.1)	25	2.6 (1.0)
Crankiness	32	2.7 (0.8)	18	2.7 (0.9)
Impatience	31	2.8 (1.1)	21	2.9 (1.0)
Decreased confidence	31	2.7 (0.8)	30	2.6 (0.9)
Feeling of losing control	22	3.1 (1.1)	23	2.7 (1.1)
Quick temper	26	2.8 (0.9)	21	2.7 (0.9)
Emotional issues	27	2.6 (0.7)	20	2.5 (0.7)
Fear of progression of disease	33	3.2 (1.2)	37	3.0 (0.9)
Fear of choking	22	3.1 (1.1)	19	3.0 (0.9)
Nervousness	26	2.9 (1.1)	22	2.6 (1.0)
Depression	22	2.7 (0.9)	21	2.4 (0.7)
Fear of a worsening ability to think	33	3.0 (1.1)	36	2.8 (1.0)
Obsessive thoughts	18	2.8 (1.0)	13	2.5 (0.8)
Fear of falling	26	2.9 (1.0)	24	2.8 (0.9)

[a]For each item in this analysis, "affected" participants were defined as those having baseline scores ≥2 (rating of "it affects my life a little" or worse).
[b]Score range per item: 0 ("I don't experience this") to 5 ("it affects my life severely").
HD-HI, Huntington's Disease Health Index; SD, standard deviation.

- In affected participants, mean changes from baseline to weeks 10 and 12 in HD-HI emotional health items generally favored valbenazine over placebo (**Figure 2**)
  - At week 12, a greater magnitude of improvement with valbenazine relative to placebo was found for most items, with statistical significance (analyzed post hoc) for the following: anger, feeling of being overwhelmed, fluctuating mood, reduced enjoyment with activities, emotional outbursts, frustration, anxiety, and crankiness (all $P<0.05$ for valbenazine versus placebo)
  - Week 12 improvements with valbenazine were generally comparable to or greater than improvements observed at week 10

Figure 2. Mean Changes in HD-HI Emotional Health Subscale Items (Affected Participants[a])



[a]$P<0.05$ for valbenazine versus placebo.
[b]For each item in this analysis, "affected" participants were defined as those having baseline scores ≥2 (rating of "it affects my life a little" or worse).
HD-HI, Huntington's Disease Health Index.

SAFETY OUTCOMES

- In the safety analysis set (N=127), psychiatric-related TEAEs that occurred in >2% of valbenazine-treated participants included depression (3.1% vs 1.6% for placebo), and anxiety (3.1% vs 0%)
  - A TEAE of suicidal ideation was reported in 1 placebo-treated participant and no valbenazine-treated participants
- Consistent with TEAE findings, C-SSRS shift analyses indicated no worsening of suicidal ideation with valbenazine treatment at any post-baseline study visit (**Table 3**)

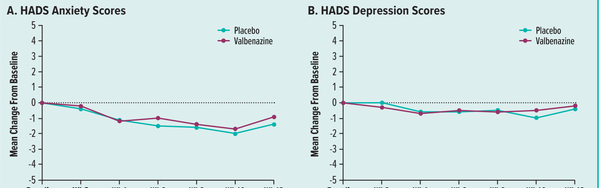
Table 3. C-SSRS Shifts From Baseline (Safety Analysis Set)

		Maximum Suicidal Ideation Score (Day 1 through Week 12)[a]					
	Baseline Score	0	1	2	3	4	5
Placebo (n=63)[b]	0	58	2	0	0	0	0
	1	0	2	0	0	0	0
Valbenazine (n=64)	0	63	0	0	0	0	0
	1	0	1	0	0	0	0

Shaded boxes indicate no worsening from baseline in C-SSRS suicidal ideation score.
[a]Maximum suicidal ideation score at any time during KINECT-HD. 0=no suicidal ideation, 1=wish to be dead, 2=non-specific active suicidal thoughts, 3=active suicidal ideation with any methods (not plan) without intent to act, 4=active suicidal ideation with some intent to act, without specific plan, 5=active suicidal ideation with specific plan and intent.
[b]One participant receiving placebo was missing either a baseline score or all post-baseline scores and was not included in the table.
C-SSRS, Columbia-Suicide Severity Rating Scale.

- At all post-baseline study visits, mean changes from baseline in HADS anxiety and depression scores were minimal in both treatment groups (**Figure 3**)

Figure 3. Mean Changes From Baseline in HADS Scores (Safety Analysis Set)



Lower scores indicate less anxiety or depression.
HADS, Hospital Anxiety and Depression Scale; PBO, placebo; VBZ, valbenazine; wk, week.

LIMITATIONS

- The 12-week study duration, designed to evaluate change in chorea, may not be sufficient to detect changes in emotional health with valbenazine
- Individuals who had untreated or uncontrolled psychiatric symptoms (including those with a HADS depression score ≥11) or were taking antipsychotic medications were excluded from the study; thus, these analyses may be limited in their ability to detect effects related to depression or depressed mood and may not represent outcomes for the real-world treatment population
- All HD-HI subscales and items have been validated for internal consistency and reliability as well as ability to differentiate between individuals with high HD-related burden versus low burden[7]; however, the ability of the emotional health subscale to longitudinally assess changes in emotional health in those with HD has not previously been validated
- For this analysis, change in HD-HI emotional health item scores was evaluated for participants with ratings of "it affects my life a little" or worse; future sensitivity analyses in participants with higher symptomatic severity at baseline are warranted to determine the robustness of these results
- In addition, item-level analyses for the HD-HI (efficacy assessment) were conducted post hoc, and the greater anxiety improvements with valbenazine versus placebo detected with the HD-HI were not consistent with mean changes in the HADS
- Despite these limitations, validity of the results from this post-hoc analysis is supported by the consistency of effect (i.e., observed improvement with valbenazine versus placebo at both weeks 10 and 12), along with the increased magnitude of improvement from week 10 to week 12

CONCLUSIONS

- Post-hoc analyses indicate that some aspects of emotional health may improve with 12 weeks of valbenazine treatment among "affected" individuals with HD (i.e., those with an item score rating of "it affects my life a little" or worse)
- These analyses suggest that HD-HI emotional health subscale items are sensitive to detect symptomatic improvements with therapy during a clinical trial
- Psychiatric symptoms remained stable throughout the study, and no worsening in suicidal ideation was observed with valbenazine
- The long-term valbenazine extension study (KINECT®-HD2: NCT04400331) will further explore safety, tolerability, and relationships between motor and psychiatric symptoms
- Considering the risk for suicidal ideation and behavior in individuals with HD,[8] those receiving a VMAT2 inhibitor or other medication for chorea should be regularly monitored for changes in psychiatric symptoms and emergence of suicidal thinking or behavior

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