The Huntington's Disease Health Index (HD-HI): Measuring Changes in Disease Burden in Response to Valbenazine During the KINECT®-HD Trial

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ABSTRACT DESCRIPTION

In KINECT®-HD, adults with chorea associated with Huntington's disease (HD) received once-daily valbenazine (40-80 mg) or placebo for 12 weeks. As measured by the patient-reported Huntington's Disease Health Index (HD-HI), participants receiving valbenazine experienced numerically greater improvements in subscales of mobility, abnormal movements, hand/arm function, emotional health, cognition, and social satisfaction.

INTRODUCTION

- The HD-HI is a validated, disease-specific, patient-reported outcome (PRO) designed to measure clinically meaningful changes in HD-related burden in response to therapeutic interventions[1]
- Following guidance from the US Food and Drug Administration (FDA) on PROs for clinical trials, the HD-HI was developed using input from individuals with HD to reflect the physical, mental, and social issues and symptoms that have the greatest impact[2]
- Valbenazine is a highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor that is FDA-approved for tardive dyskinesia and for chorea associated with HD[3]
- In a 12-week, randomized, double-blind, placebo-controlled clinical trial (KINECT-HD: NCT04102579),[4] valbenazine-treated participants had significant reductions in chorea as demonstrated by the following:
  - Least-squares mean changes from screening/baseline to Week 10/12 in the Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) score (-4.6 vs -1.4 for placebo; *P*<0.0001) (primary endpoint)
  - Responder status at Week 12, based on the Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) (secondary endpoints)
- KINECT-HD was also the first phase 3 trial to implement the HD-HI, the results of which are presented below

OBJECTIVES

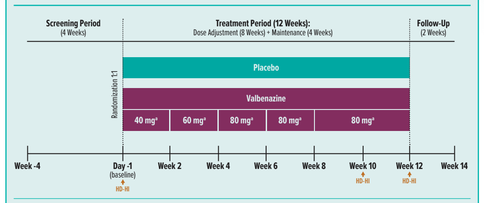
- Understand that the HD-HI is a validated, sensitive patient-reported outcome used to measure longitudinal changes in symptomatic disease-related burden in individuals with HD
- Recognize that adults with HD receiving once-daily valbenazine for their chorea reported numeric improvements in several domains of disease-related burden as measured by the HD-HI

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
  - The HD-HI was administered on Day -1 (baseline), Week 10, and Week 12 to assess patient-reported disease burden in this trial

Figure 1. Study Design



*Doses represent maximum daily doses during each 2-week interval in the dose-adjustment period and during the maintenance period.
HD-HI, Huntington's Disease Health Index.

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:
  - Serious, unstable, or untreated medical or psychiatric illness
  - Score ≥11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS)
  - Significant risk for suicidal ideation or behavior per the Columbia-Suicide Severity Rating Scale
  - Use of antipsychotics or other dopamine receptor blockers, strong CYP3A4 inducers, dopamine agonists/precursors, monoamine oxidase inhibitors, or VMAT2 inhibitors

ASSESSMENT AND ANALYSES

- The HD-HI includes 13 subscale scores and a total score
  - Subscale scores and total score range from 0 (no disease burden) to 100 (highest disease burden)
  - The total score is the weighted average of the 13 subscale scores, with weighting based on the average importance of each item within the subscales
- Observed values and score changes from baseline were summarized descriptively by treatment group and visit
- Post hoc analysis using an analysis of covariance (ANCOVA) model was performed for the change from baseline in HD-HI subscales and total score

RESULTS

- In the full analysis set (N=125), demographics and baseline characteristics were similar between treatment groups (**Table 1**)

Table 1. Demographics and Baseline Characteristics

	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)
Not Hispanic or Latino, n (%)	58 (95.1)	59 (92.2)
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)
UHDRS® scores, mean (SD)		
Total Maximal Chorea[b]	12.1 (2.8)	12.2 (2.3)
Total Motor Score[c]	31.1 (12.4)	35.7 (13.3)
Total Functional Capacity[d]	10.4 (2.1)	10.1 (2.1)
CGI-S score ≥4, n (%)[e]	28 (45.9)	33 (51.6)
PGI-S score ≥3, n (%)[e]	25 (41.0)	31 (48.4)
HADS anxiety score, mean (SD)[f]	5.4 (4.2)	4.0 (4.0)
HADS depression score, mean (SD)[f]	3.6 (3.3)	3.0 (2.6)
MoCA total score, mean (SD)[g]	24.2 (3.2)	22.9 (4.3)

[a]Additional self-reported races were as follows: Black/African American (n=1), Asian (n=1), and other unspecified (n=3).
[b]For screening/baseline (average of values from screening and baseline), per assessment by on-site study investigator. Score range: 0 to 28, with higher scores indicating more severe chorea.
[c]Score range: 0 to 124, with higher scores indicating more severe motor impairment.
[d]Score range: 0 to 13, with lower scores indicating more severe functional impairment.
[e]Represents moderate or worse severity of chorea symptoms per clinician assessment or patient self-report.
[f]Score range: 0-7 (normal), 8-10 (mild), 11-14 (moderate), 15-21 (severe).
[g]Score range: 0-9 (severe impairment), 10-17 (moderate impairment), 18-25 (mild impairment), 26-30 (normal).
CGI-S, Clinical Global Impression of Severity; HADS, Hospital Anxiety and Depression Scale; MoCA, Montreal Cognitive Assessment; PGI-S, Patient Global Impression of Severity; SD, standard deviation; UHDRS®, Unified Huntington's Disease Rating Scale.

- Among participants with available HD-HI assessments at baseline (N=122), subscale scores in the valbenazine group were slightly higher (worse) for mobility and hand/arm function and slightly lower (better) for emotional health, social satisfaction, fatigue, and cognition (**Table 2**)

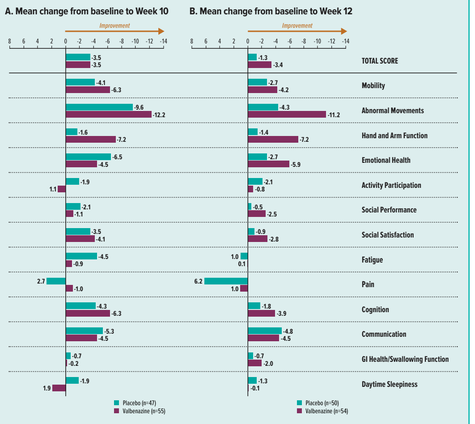
Table 2. HD-HI Scores at Baseline

	Placebo (n=58)	Valbenazine (n=64)
HD-HI total score, mean (SD)[a]	19.4 (16.2)	18.7 (17.3)
HD-HI subscales, mean (SD)[a]		
Mobility	20.7 (20.2)	24.5 (25.0)
Abnormal movements	28.5 (24.1)	27.5 (25.4)
Hand and arm function	20.1 (19.9)	24.8 (23.9)
Emotional health	21.2 (20.7)	16.6 (18.3)
Activity participation	16.0 (19.0)	17.6 (21.4)
Social performance	17.9 (18.5)	18.0 (20.5)
Social satisfaction	17.4 (17.8)	14.3 (18.4)
Fatigue	17.8 (20.2)	14.7 (20.9)
Pain	9.4 (14.1)	9.9 (19.8)
Cognition	26.2 (23.6)	23.1 (23.4)
Communication	23.4 (20.6)	23.7 (20.6)
GI health/swallowing function	14.9 (20.0)	12.8 (18.4)
Daytime sleepiness	16.2 (20.9)	16.0 (22.5)

[a]Score range: 0 (no disease burden) to 100 (highest degree of disease burden).
GI, gastrointestinal; HD-HI, Huntington's Disease Health Index; SD, standard deviation.

- **Figure 2** presents mean changes from baseline to Week 10 and Week 12 in HD-HI total score and subscale scores (prespecified exploratory endpoint)
  - Numerical changes at Week 12 were comparable to those at Week 10 and indicated greater magnitude of improvement with valbenazine versus placebo in the total score and in 8 of 13 subscale scores: mobility, abnormal movements, hand and arm function, emotional health, social performance, social satisfaction, cognition, and gastrointestinal health/swallowing function
  - At Week 12, there was no meaningful worsening in fatigue and daytime sleepiness in valbenazine-treated participants
  - Impact of pain on overall disease burden worsened from Week 10 to Week 12 and was reported with greater magnitude in the placebo group

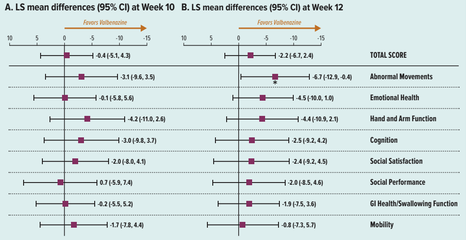
Figure 2. Mean Changes from Baseline for HD-HI Total Score and Subscale Scores (Prespecified Exploratory Endpoint)



GI, gastrointestinal; HD-HI, Huntington's Disease Health Index.

- Among the 8 subscales with greater valbenazine improvements relative to placebo at Week 12, post hoc ANCOVA analyses indicated that those with the largest least-squares mean differences between treatment groups (LSMD >2.0) were abnormal movements, emotional health, hand and arm function, cognition, and social satisfaction (**Figure 3**)
  - A statistically significant difference was found for abnormal movements at Week 12 (*P*=0.0379)

Figure 3. Treatment-Group Differences in HD-HI Score Changes (Post Hoc Analysis)[a]



*P<0.05 for valbenazine versus placebo.
[a]For total score and subscale scores that indicated a favorable improvement with valbenazine at Week 12.
CI, confidence interval; GI, gastrointestinal; HD-HI, Huntington's Disease Health Index; LS, least-squares.

CONCLUSIONS

- The patient-reported HD-HI scale was used in KINECT-HD to measure longitudinal changes in symptomatic disease burden in response to treatment for chorea
- In this study, greater reduction in HD-related disease burden was reported with valbenazine versus placebo in domains that are particularly affected among individuals experiencing chorea (abnormal movements, hand and arm function, mobility)
- Greater improvements with valbenazine relative to placebo were also found in domains related to emotional and social well-being, cognition, and gastrointestinal health/swallowing
- These results indicate that the HD-HI was a sensitive measure of patient-reported, disease-related burden in this study population and a useful tool for capturing such changes in future clinical trials of HD therapies

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Please contact medinfo@neurocrine.com with any questions.

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