KINECT™-HD & KINECT™-HD2 Overview

NEUROCRINE® BIOSCIENCES

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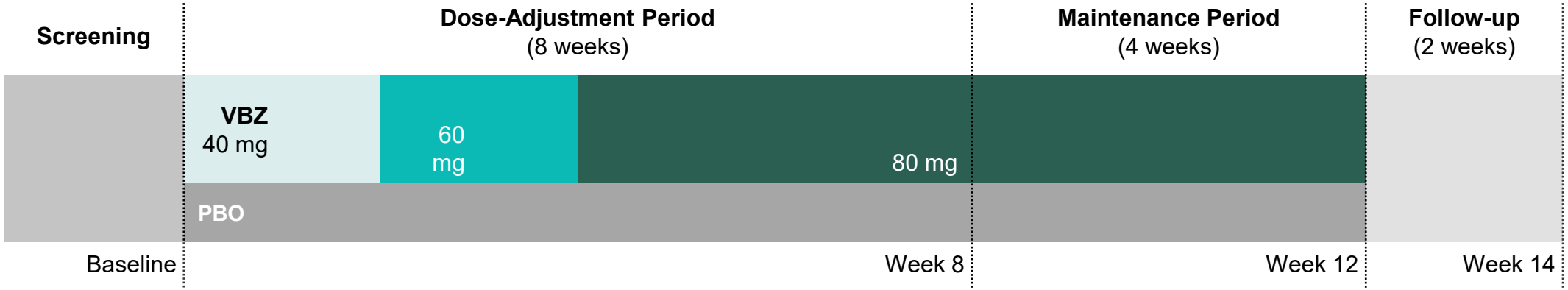
KINECT™-HD

Safety and efficacy of valbenazine for the treatment of chorea associated with Huntington disease: a phase 3, randomized, double-blind, placebo-controlled trial

Study Design[1,2]

KINECT™-HD is a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of once-daily valbenazine for the treatment of chorea associated with Huntington disease (HD)



- **4-week** screening period
- **12-week** treatment period
- Final study visit 2 weeks following the final dose of study drug

Valbenazine dosing started at **40 mg once daily**, with 20-mg increases allowed as tolerated at the end of Weeks 2, 4, and 6 to a target dose of **80 mg once daily**; dose reductions were allowed

- **128 adult male and females**
- Randomized 1:1
- US/Canada

ClinicalTrials.gov identifier: NCT04102579

Valbenazine has not been approved by the FDA for the treatment of chorea associated with HD

FDA, US Food and Drug Administration; PBO, placebo; UHDRS, Unified Huntington's Disease Rating Scale; TMC, Total Maximal Chorea; VBZ, valbenazine.

1. Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.| 2. Clinicaltrials.gov. Accessed June 23, 2023. https://clinicaltrials.gov/ct2/show/NCT04102579?cond=NCT04102579&draw=2&rank=1.

Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Adults18 - 75 years old with a clinical diagnosis of HD with chorea
- Expanded CAG repeat (≥37) in huntingtin (HTT) gene
- TMC score ≥8 at screening and baseline
- TFC score ≥5 at screening*

Key Exclusion Criteria

- Serious, unstable, untreated or undertreated medical or psychiatric illness
- Hospital Anxiety and Depression Scale (HADS) depression subscale score ≥11
- Significant risk of suicide, including any recent history (within past 3 months) of active suicidal ideation with intent or behavior per the Columbia-Suicide Severity Rating Scale (C-SSRS)
- History or evidence of long QT syndrome or any other important cardiac condition or abnormality
- Clinically manifest dysphagia, defined as a Swallowing Disturbance Questionnaire (SDQ) score ≥11

*Score of 5-10 required a reliable caregiver to ensure drug administration and attendance at study visits. AV, atrioventricular; CAG, cytosine, adenine, and guanine; HD, Huntington disease; TFC, Total Functional Capacity; TMC, Total Maximal Chorea; VMAT2, vesicular monoamine transporter.

Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Outcomes

Primary Efficacy Endpoint

- Change from baseline (average of screening and baseline score) to maintenance (average of Week 10 and Week 12) in Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) score as assessed by on-site study investigators

Secondary Efficacy Endpoints

- Response status* at Week 12:
  - Clinical Global Impression of Change (CGI-C)
  - Patient Global Impression of Change (PGI-C)
- Change from Baseline to Week 12 in the Quality of Life in Neurological Disorders (Neuro-QoL)
  - Upper Extremity Function T-score
  - Lower Extremity Function T-score

Safety Endpoints

- AEs, clinical laboratory tests, vital signs, physical examinations, ECG, Columbia-Suicide Severity Rating Scale (C-SSRS), Barnes Akathisia Rating Scale (BARS), Hospital Anxiety and Depression Scale (HADS), UHDRS motor score (items for parkinsonism)

*Participants with CGI-C or PGI-C scores of either a 1 ("very much improved") or a 2 ("much improved") were classified as responders.
AEs, adverse events; ECG, electrocardiogram.

Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Outcomes Cont.

Prespecified Exploratory Endpoints in the Full Analysis Set

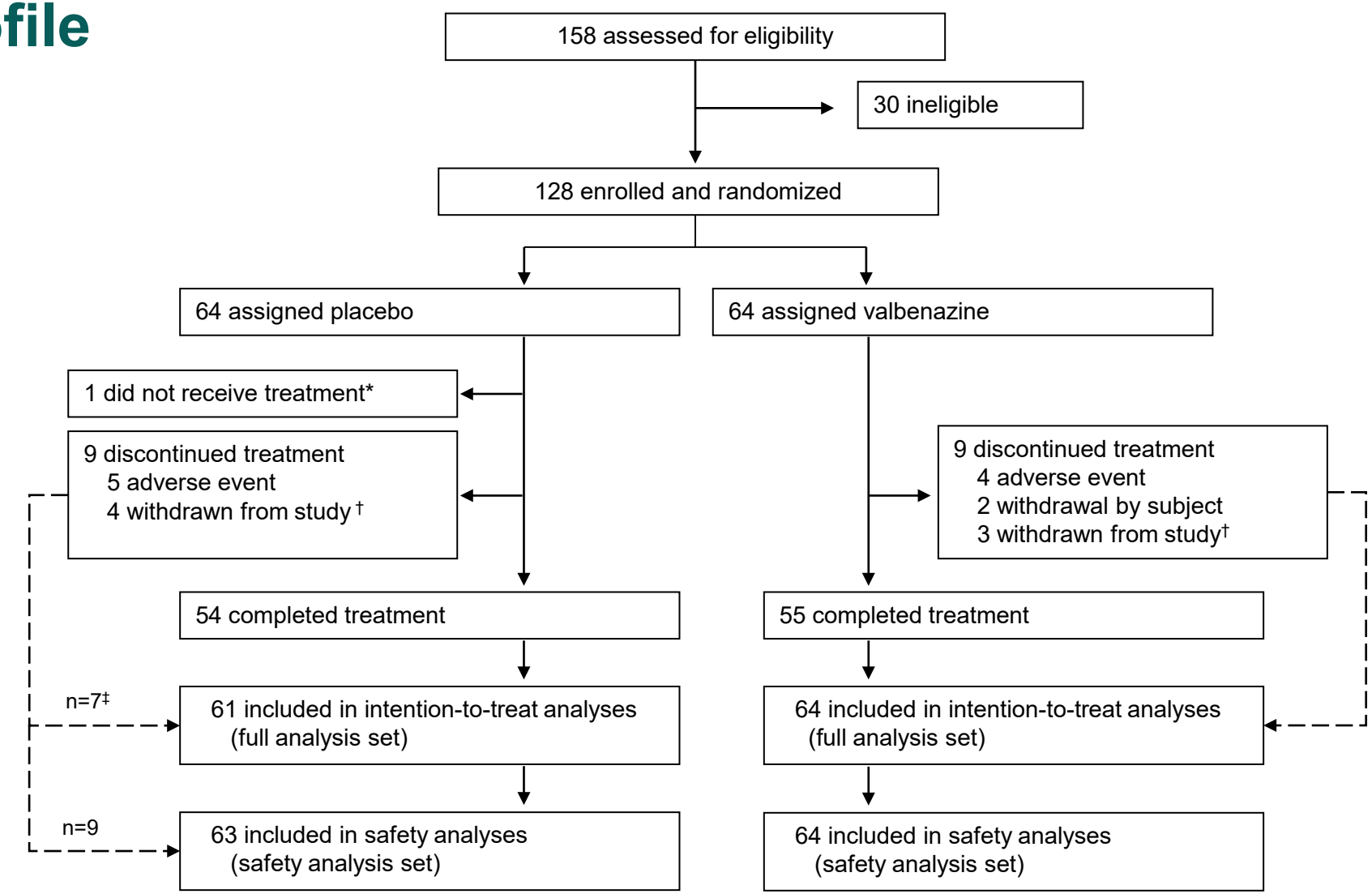
The following are some of the prespecified efficacy endpoints for KINECT™-HD

- Changes from the screening period baseline to each postbaseline study visit (Weeks 2 through 12) in the TMC based on site assessments
- Changes from the screening period baseline to maintenance (the average of the Week 10 and Week 12 assessments) in the TMC based on video recording central rater assessments
- CGI-C response statuses* at Weeks 2 through 10
- PGI-C response statuses* at Weeks 2 through 10
- Huntington Disease Health Index (HD-HI) at Week 10 and Week 12
- Anosognosia Scale (AS) at Week 12

*Participants with CGI-C or PGI-C scores of either a 1 ("very much improved") or a 2 ("much improved") were classified as responders.
CGI-C, Clinical Global Impression of Change; PGI-C, Patient Global Impression of Change; TMC, total maximal chorea.

Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Trial Profile



*Participant was excluded from intention-to-treat and safety analyses. †Withdrawn from the study because of closure of study site during the study pause because of COVID-19. ‡Two participants in the placebo group who did not have a Unified Huntington's Disease Rating Scale Total Maximal Chorea score at baseline or after baseline were included in the safety analyses but excluded from intention-to-treat analyses.

Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Baseline Demographics

Full Analysis Set	Placebo (n=61)	Valbenazine (n=64)
Age, years	53.3 (11.4)	54.1 (10.1)
Sex		
Female	35 (57%)	33 (52%)
Male	26 (43%)	31 (48%)
Race		
White	60 (98%)	60 (94%)
Black or African American	0	1 (2%)
Asian	0	1(2%)
Other (not specified)	1 (2%)	2 (3%)
Ethnicity		
Hispanic or Latino	3 (5%)	5 (8%)
Not Hispanic or Latino	58 (95%)	59 (92%)
Body mass index, kg/m^2	27.4 (5.7)	26.6 (5.6)
CAG repeat length	43.3 (3.1)	43.5 (3.3)
UHDRS® TMC score*	12.1 (2.8)	12.2 (2.3)
CGI-S score ≥4†	28 (46%)	33 (52%)
PGI-S score ≥3†	25 (41%)	31 (48%)
SDQ total score	5.2 (6.2)	4.9 (6.2)
MoCA score	24.2 (3.2)	22.9 (4.3)

- Baseline demographics were similar between treatment groups
- Almost half of all participants had moderate or severe chorea, with 61 (49%) having a CGI-S score of 4 or higher and 56 (45%) having a PGI-S score of 3 or higher

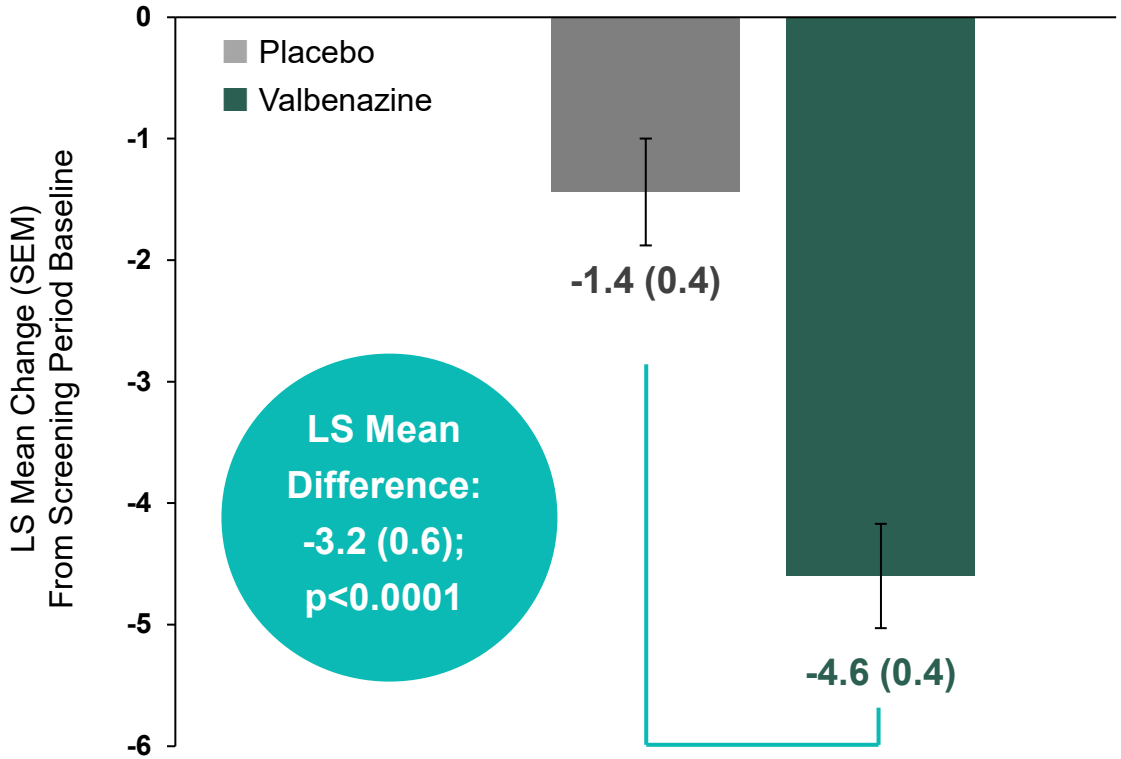
Data are mean (SD) or n (%). *Based on the average of the values from screening and baseline of each participant, as assessed by the on-site study investigator. †Scores indicate moderate or worse severity.

CGI-S, Clinical Global Impression of Severity; MoCA, Montreal Cognitive Assessment; PGI-S, Patient Global Impression of Severity; SD, standard deviation; SDQ, Swallowing Disturbance Questionnaire; TMC, total maximal chorea; UHDRS®, Unified Huntington's Disease Rating Scale.

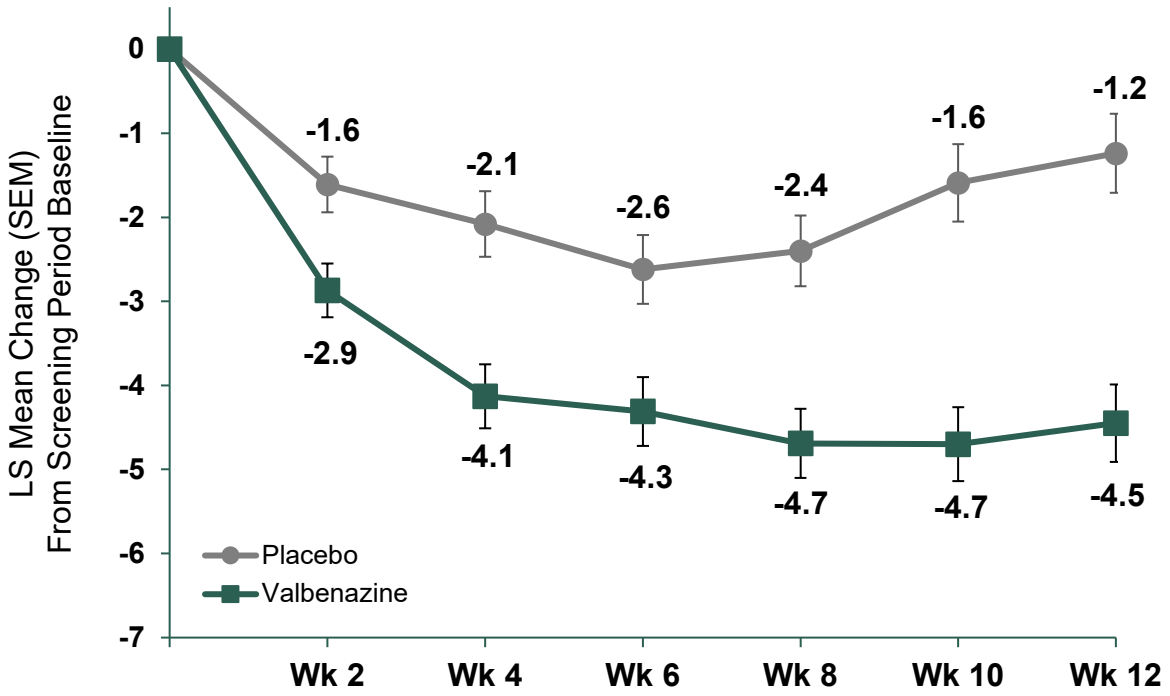
Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Mean Changes in UHDRS® Total Maximal Chorea (TMC)

KINECT™-HD met its primary endpoint with a **statistically significant reduction in chorea** with valbenazine versus placebo



Prespecified Exploratory Endpoint: UHDRS TMC mean changes over time



The screening and baseline period was defined as the average of values from screening and baseline visits. The maintenance period was defined as the average of values from week 10 and week 12.
Error bars represent SEMs; numbers in parentheses represent 95% CIs. SEM=standard error of the mean. UHDRS=Unified Huntington's Disease Rating Scale.LS, least-squares; SEM, standard error of the mean; UHDRS®, Unified Huntington's Disease Rating Scale; Wk, week.

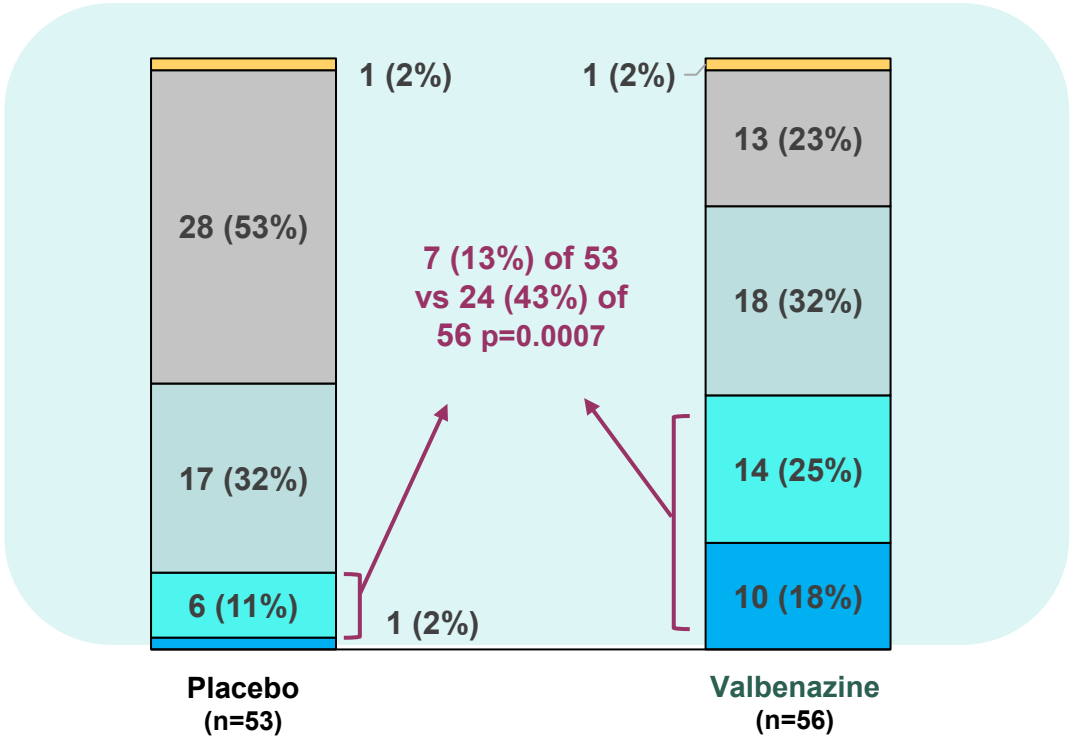
Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Secondary Endpoints

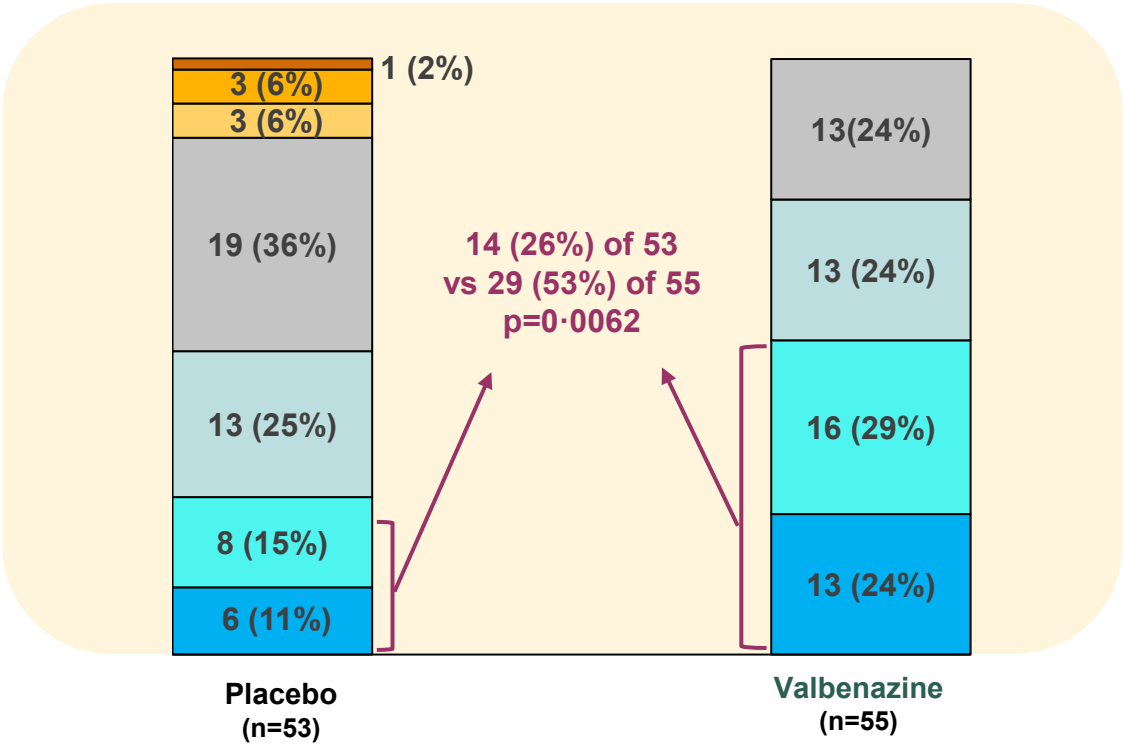
CGI-C and PGI-C Response at Week 12

- The proportion of participants with clinician and self-rated global improvements (“much improved” or better) was significantly higher with valbenazine versus placebo at Week 12

CGI-C Response



PGI-C Response



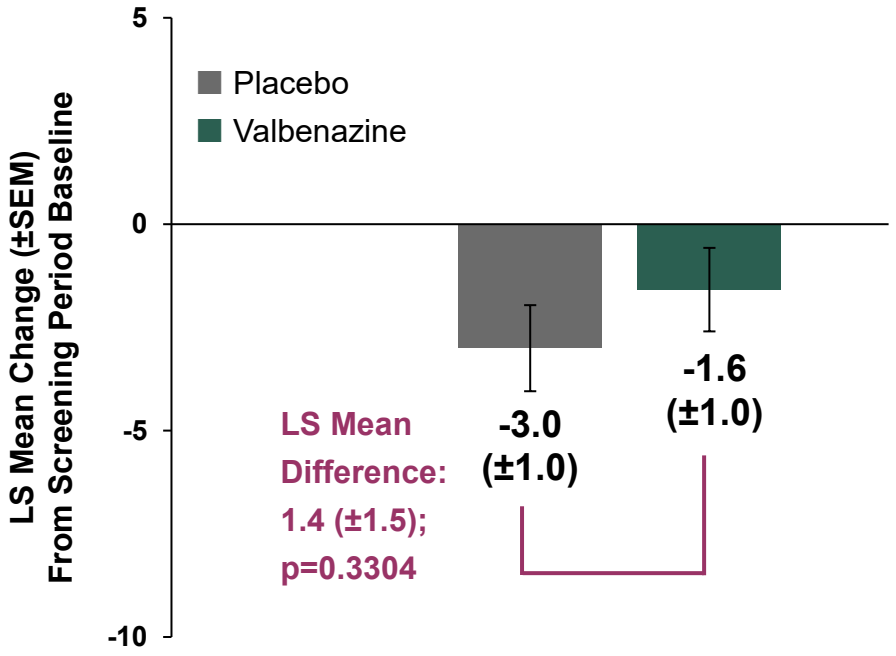
Very much improved | Much improved | Minimally improved | No change | Minimally worse | Much worse | Very much worse

Graphs represent the distribution of CGI-C and PGI-C scores by treatment group, with purple brackets indicating the percentage and number of participants who met the threshold for good clinical response, defined as a rating of “much improved” or “very much improved” from baseline. CGI-C, Clinical Global Impression of Change; PGI-C, Patient Global Impression of Change. Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

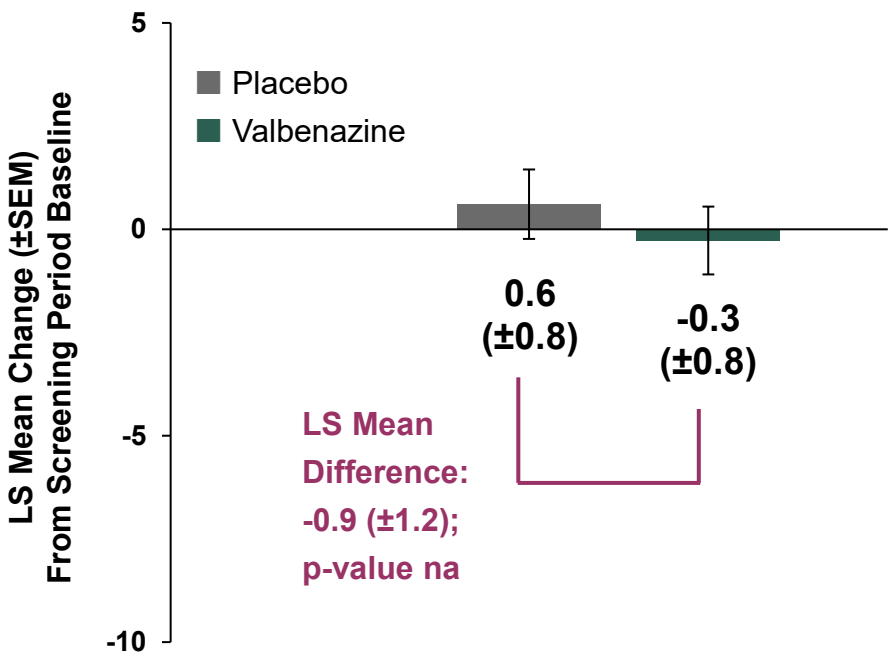
Secondary Endpoint Cont.

- Change from baseline to Week 12 was not statistically significant for the Neuro-QoL Upper Extremity Function (UEF) T-score
- Statistical analysis for Lower Extremity Function (LEF) was not conducted per the fixed-sequence testing procedure
  - Most participants' scores were at or near maximum values at baseline, which might have limited the sensitivity of the Neuro-QoL instrument to detect change in this study population.

Neuro-QoL UEF T-score



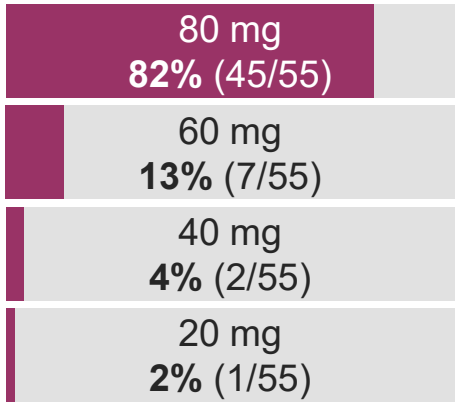
Neuro-QoL LEF T-score



LS, least squares; Neuro QoL, Quality of Life in Neurological Disorders; SEM, standard error mean. Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Safety: Treatment Emergent Adverse Events

- Of the 55 participants treated with valbenazine who reached the week 12 visit, most were taking 80 mg



- The most commonly reported TEAEs with valbenazine were somnolence, fatigue, and falls
- The valbenazine group had 1 serious TEAE of angioedema
  - Assessed by the investigator as unlikely related to treatment, possibly due to allergic reaction after shellfish consumption; no dose change or study withdrawal

	Placebo (n=63)	Valbenazine (n=64)
Summary, n (%)		
Any TEAE	40 (64%)	49 (77%)
Serious TEAE*	2 (3%)	1 (2%)
TEAE leading to dose reduction	3 (5%)	9 (14%)
TEAE leading to study drug discontinuation	4 (6%)	5 (8%)
TEAE resulting in death	1 (2%)†	0
Common TEAEs‡		
Somnolence	2 (3%)	10 (16%)
Fatigue	6 (10%)	9 (14%)
Fall	8 (13%)	8 (13%)
Urticaria	0	6 (9%)
Rash	0	5 (8%)
Akathisia	3 (5%)	4 (6%)
Pain in extremity	2 (3%)	3 (5%)
Diarrhoea	1 (2%)	3 (5%)
Back pain	0	3 (5%)
Middle insomnia	0	3 (5%)
Nausea	0	3 (5%)
Headache	3 (5%)	2 (3%)
Constipation	3 (5%)	0
Hypertension	3 (5%)	0
Myalgia	3 (5%)	0
Nasopharyngitis	3 (5%)	0

TEAE, treatment emergent adverse event

*Serious TEAEs occurred in two participants in the placebo group (colon cancer and psychosis) and in one participant in the valbenazine group (angioedema caused by an allergic reaction to shellfish). †Death caused by colon cancer, judged by the investigator as being unlikely to be related to the study drug. ‡Reported in 4% or more of participants in either treatment group. Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Safety Cont.

- Mean changes from baseline to week 12 in additional safety scales were similar between treatment groups
  - No worsening in anxiety or depression (HADS), akathisia (BARS), or parkinsonism (items from UHDRS motor assessment) with either valbenazine or placebo.

- There was no evidence for treatment-emergent suicidal ideation or behavior with valbenazine, with no participants reporting suicidal ideation as a TEAE and no participants having an increase in suicidal ideation or any suicidal behavior on the C-SSRS

- No clinically meaningful differences between treatment groups were found for vital signs, electrocardiograms (including QTcF), or laboratory tests

- Mean changes from baseline to week 12 (SD) in orthostatic blood pressure (mmHg) were small in both treatment groups, for both
  - Systolic blood pressure (valbenazine, –1·8 [15·9]; placebo, –0·8 [11·7])
  - Diastolic blood pressure (valbenazine, 0·8 [12·1]; placebo, –2·5 [10·5])

SD, standard deviation; TEAE, treatment emergent adverse event

Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Summary

- Valbenazine met the primary endpoint of significant improvement in chorea severity vs placebo ($p<0.001$) with improvements as early as week 2
- Clinicians (CGI-C) and patients (PGI-C) reported clinically meaningful results with valbenazine versus placebo
- TEAEs that affected more than 10% of patients treated with valbenazine were somnolence, fatigue, and falls.
  - Some hypersensitivity reactions (urticaria and rash) were reported with valbenazine, and use of valbenazine should be avoided in individuals with a history of hypersensitivity to this medication or any of its formulation components, consistent with current prescribing recommendations
- There was no evidence of treatment-emergent suicidal behavior or worsening of suicidal ideation with valbenazine, and HADS depression and anxiety scores remained stable
  - However, given the risk for suicidal ideation and suicide attempts among individuals with Huntington's disease, all patients taking a VMAT2 inhibitor or other medication for chorea should be monitored regularly for suicidal thoughts and behaviors

Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

KINECT™-HD2

Phase 3, open-label study to evaluate the long-term safety and tolerability of valbenazine, and to provide participants continued access to valbenazine for the treatment of chorea associated with Huntington disease

Study Design

Phase 3, open-label study to evaluate the long-term safety and tolerability of valbenazine, and to provide participants continued access to valbenazine for the treatment of chorea associated with Huntington disease[1,2]

Currently recruiting

Approximately **150 adult males and females** will be enrolled

Primary assessment: Emergence of TEAEs

Valbenazine has not been approved by the FDA for the treatment of chorea associated with HD

For more information on the study or how to enroll patients, please scan the QR code or visit **https://huntingtonstudygroup.org/current-clinical-trials/kinect-hd2/**

ET, end of treatment; FA, final assessment; FDA, US Food and Drug Administration; HD, Huntington disease; TEAE, treatment-emergent adverse event; VBZ, valbenazine.

1. ClinicalTrials.gov. Accessed June 20, 2023. https://clinicaltrials.gov/ct2/show/NCT04400331. | 2. Neurocrine Biosciences. VBZ-HD-0001. Data on file.

KINECT™-HD2 Study

Key inclusion criteria

- Participated in KINECT™-HD[a] **and**
  - Study dosing completion,[b] **or**
  - Early termination of KINECT™-HD for administrative reasons due to COVID-19[c]
- **Or** did not participate in KINECT™-HD **and** met criteria as set forth in KINECT™-HD

Key Exclusion Criteria

- Received an investigational drug within 30 days before the baseline visit or plan to use an investigational drug (other than VBZ) during the study
- Known history of long QT syndrome, cardiac tachyarrhythmia, left bundle-branch block, AV block, uncontrolled bradyarrhythmia, or heart failure
- Unstable or serious medical or psychiatric illness
- Significant risk of suicidal behavior
- History of substance dependence or abuse

AV, atrioventricular; ET, end of treatment; FA, final assessment; FDA, US Food and Drug Administration; HD, Huntington disease; VBZ, valbenazine. [a]KINECT™-HD is a phase 3, randomized, double-blind, placebo-controlled study completed in October 2021. [b]As demonstrated by completed study drug dosing through the follow-up visit. [c]Site closure related to COVID-19.
ClinicalTrials.gov. Accessed June 20, 2023. https://clinicaltrials.gov/ct2/show/NCT04102579.

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