Safety and efficacy of valbenazine for the treatment of chorea associated with Huntington's disease (KINECT-HD): a phase 3, randomised, double-blind, placebo-controlled trial

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See Comment page 459

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Summary

Background Valbenazine is a highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor approved for treatment of tardive dyskinesia. To address the ongoing need for improved symptomatic treatments for individuals with Huntington's disease, valbenazine was evaluated for the treatment of chorea associated with Huntington's disease.

Methods KINECT-HD (NCT04102579) was a phase 3, randomised, double-blind, placebo-controlled trial, performed in 46 Huntington Study Group sites in the USA and Canada. The study included adults with genetically confirmed Huntington's disease and chorea (Unified Huntington's Disease Rating Scale [UHDRS] Total Maximal Chorea [TMC] score of 8 or higher) who were randomly assigned (1:1) via an interactive web response system (with no stratification or minimisation) to oral placebo or valbenazine (≤80 mg, as tolerated) for 12 weeks of double-blinded treatment. The primary endpoint was a least-squares mean change in UHDRS TMC score from the screening and baseline period (based on the average of screening and baseline values for each participant) to the maintenance period (based on the average of week 10 and 12 values for each participant) in the full-analysis set using a mixed-effects model for repeated measures. Safety assessments included treatment-emergent adverse events, vital signs, electrocardiograms, laboratory tests, clinical tests for parkinsonism, and psychiatric assessments. The double-blind placebo-controlled period of KINECT-HD has been completed, and an open-label extension period is ongoing.

Findings KINECT-HD was performed from Nov 13, 2019, to Oct 26, 2021. Of 128 randomly assigned participants, 125 were included in the full-analysis set (64 assigned to valbenazine, 61 assigned to placebo) and 127 were included in the safety-analysis set (64 assigned to valbenazine, 63 assigned to placebo). The full-analysis set included 68 women and 57 men. Least-squares mean changes from the screening and baseline period to the maintenance period in the UHDRS TMC score were –4·6 for valbenazine and –1·4 for placebo (least-squares mean difference –3·2, 95% CI –4·4 to –2·0; p<0·0001). The most commonly reported treatment-emergent adverse event was somnolence (ten [16%] with valbenazine, two [3%] with placebo). Serious treatment-emergent adverse events were reported in two participants in the placebo group (colon cancer and psychosis) and one participant in the valbenazine group (angioedema because of allergic reaction to shellfish). No clinically important ch anges in vital signs, electrocardiograms, or laboratory tests were found. No suicidal behaviour or worsening of suicidal ideation was reported in participants treated with valbenazine.

Interpretation In individuals with Huntington's disease, valbenazine resulted in improvement in chorea compared with placebo and was well tolerated. Continued research is needed to confirm the long-term safety and effectiveness of this medication throughout the disease course in individuals with Huntington's disease-related chorea.

Funding Neurocrine Biosciences.

Introduction

Huntington's disease is an inherited autosomal-dominant disease caused by a pathogenic CAG expansion in the *HTT* gene, which leads to neurodegeneration that results in psychiatric, motor, and cognitive symptoms.[1,2] Although psychiatric symptoms can vary over time, motor and cognitive symptoms predictably worsen as the disease progresses.[3] As such, patients with Huntington's disease experience a progressive loss of functional independence and increased reliance on caregivers for support.[4,5]

Approximately 90% of individuals with adult-onset Huntington's disease exhibit chorea during their disease course.[6] Chorea is described as an involuntary, purposeless movement that flows from one body part to the next. Chorea can contribute to imbalance, falls, and impaired

Research in context

Evidence before this study

We searched for English-language publications that were indexed in PubMed from Jan 1, 2000, to Apr 11, 2023. We used the following search string, excluding duplicate results, narrative review articles, letters, and studies that did not focus on chorea as the primary outcome of interest: Huntington [title] AND (VMAT2 OR deutetrabenazine OR tetrabenazine). This search yielded five publications: three for tetrabenazine (a randomised controlled trial, an extension study, and a randomised withdrawal study) and two for deutetrabenazine (a randomised controlled trial and an extension study). The search also yielded a 2009 Cochrane systematic review with meta-analysis, which concluded that tetrabenazine was the only medication (at the time of publication) to show clear efficacy for controlling chorea associated with Huntington's disease. More recent support for vesicular monoamine transporter 2 (VMAT2) inhibitors, published after KINECT-HD was initiated, can be found in a 2022 evidence-based review from the International Parkinson and Movement Disorder Society.

Added value of this study

Valbenazine is a novel VMAT2 inhibitor that was approved in 2017 by the US Food and Drug Administration for the treatment of tardive dyskinesia in adults. Inhibition of VMAT2 has been shown to reduce chorea associated with Huntington's disease. Although two VMAT2 inhibitors are currently approved for chorea associated with Huntington's disease (tetrabenazine and deutetrabenazine), there remains a need for improved symptomatic treatments in Huntington's disease. Both tetrabenazine and deutetrabenazine are metabolised into four dihydrotetrabenazine stereoisomers, which have varying degrees of affinity for VMAT2. By contrast, valbenazine produces only the [+]-α-dihydrotetrabenazine stereoisomer, which has the strongest affinity for VMAT2. Furthermore, valbenazine itself binds to VMAT2 and is therefore considered a pharmacologically active parent drug. Moreover, the pharmacokinetic profile of valbenazine allows for once-per-day dosing and a relatively short period from initiation of treatment to reach effective dosing. Therefore, KINECT-HD was designed as a randomised, double-blind, placebo-controlled, pivotal phase 3 study to evaluate the efficacy and safety of valbenazine for chorea associated with Huntington's disease. Notable aspects of this study include the use as exploratory endpoints of an Huntington's disease-specific Anosognosia Scale and the implementation of the Huntington's Disease Health Index, a novel, multidimensional, outcome validated for assessing patient-reported disease burden in individuals with Huntington's disease.

Implications of all the available evidence

KINECT-HD is, to our knowledge, the first phase 3 trial of valbenazine for chorea associated with Huntington's disease. The positive results provide evidence for valbenazine as an effective and well tolerated potential treatment option for patients with chorea associated with Huntington's disease. Continued research is needed to confirm the long-term safety and effectiveness of this medication throughout the disease course in individuals with Huntington's disease-related chorea.

dexterity and coordination. Furthermore, Huntington's disease-related chorea is associated with low rates of employment, social isolation, and the need for caregiver assistance.[5,7]

Hyperdopaminergic states have been implicated in causing hyperkinetic movements such as chorea. Therefore, current pharmacological approaches aim to attenuate chorea either by decreasing or modifying striatal dopaminergic activity through antagonism of postsynaptic receptors (eg, antipsychotic treatment) or by inhibiting presynaptic vesicular monoamine transporter 2 (VMAT2).[8] Both first-generation and second-generation antipsychotics are often prescribed to target the behavioural or neuropsychiatric symptoms of Huntington's disease, and they are also used as off-label treatments for chorea; by contrast, VMAT2 inhibitors are specifically indicated for chorea. VMAT2 facilitates the transport of dopamine, norepinephrine, and serotonin from the cytoplasm into presynaptic vesicles; inhibition of VMAT2 decreases the amount of presynaptic dopamine released, thus leading to a depleted state. On the basis of evidence from randomised controlled trials,[9,10] two VMAT2 inhibitors, tetrabenazine and deutetrabenazine, are approved by the US Food and Drug Administration (FDA) for treating chorea associated with Huntington's disease and are marketed in several countries.

Although tetrabenazine and deutetrabenazine have clearly demonstrated efficacy in treating chorea, some individuals with Huntington's disease might need or want to try other treatments for tolerability reasons or for easier titration and dosing. The need for continued advancement in the symptomatic treatment of chorea led to KINECT-HD (NCT04102579), a phase 3 study of valbenazine for chorea associated with Huntington's disease. Valbenazine, which is approved for the treatment of tardive dyskinesia, has a strong affinity and high selectivity for VMAT2, along with minimal off-target binding. These properties are driven by the hydrolysis of valbenazine into its single primary active metabolite, [+]-α-dihydrotetrabenazine, which has stronger affinity to VMAT2 than the other dihydrotetrabenazine stereoisomers ([-]-α, [+]-β, and [-]-β).[11–13] Valbenazine and its active metabolite have half-lives of 15–22 h that allow for dosing once per day.[14,15] Given the pharmacological profile of valbenazine, KINECT-HD was initiated to evaluate this medication for the treatment of chorea associated with Huntington's disease.

Methods

Study design

KINECT-HD was a phase 3, randomised, double-blind, placebo-controlled trial that assessed the efficacy, safety, and tolerability of valbenazine for the treatment of chorea associated with Huntington's disease. The study included a 12-week, double-blind treatment period and a follow up visit 2 weeks after the final dose of study drug (appendix p 8).

See Online for appendix

The study was performed at 46 movement disorder centres in the USA and Canada, all of which were credentialed by the Huntington Study Group (HSG). The final protocol was reviewed and approved by the independent ethics committee and institutional review board at each site before initiation of the study. KINECT-HD adhered to established principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practices, the US Code of Federal Regulations, FDA guidelines, Health Canada guidelines, and the Canada Food and Drugs Act and Regulations.

For the **Huntington Study Group** see https://Huntingtonstudygroup.org/hsg-credentialing/

Participants

A full list of eligibility criteria is provided in the appendix (pp 12–14). Participants were adults, aged 18–75 years, who met the following inclusion criteria: a Unified Huntington's Disease Rating Scale (UHDRS) Total Maximal Chorea (TMC) score of 8 or higher at the screening and baseline assessments; diagnosis of motor manifest Huntington's disease at or before screening; genetic diagnosis of Huntington's disease with an expanded CAG repeat (≥37 repeats) in the *HTT* gene; and a UHDRS Total Functional Capacity score of 5 or higher at screening, with a score of 5 to 10 requiring a reliable caregiver to ensure drug administration and attendance at study visits. Participants were required to demonstrate the capacity to provide informed consent, based on the University of California, San Diego Brief Assessment of Capacity to Consent. All participants provided informed and written consent before initiation of any study procedure.

Individuals were excluded from the study if they met any of the following criteria: serious, unstable, untreated, or undertreated medical or psychiatric illness; Hospital Anxiety and Depression Scale (HADS) depression subscale score of 11 or higher; substantial risk of suicide, including any recent history (within the past 3 months) of active suicidal ideation with intent or behaviour per the Columbia-Suicide Severity Rating Scale (C-SSRS); history or evidence of long QT syndrome, QT interval (with Fridericia's correction [QTcF]) higher than 450 ms (male individuals) or higher than 470 ms (female individuals), or any other important cardiac condition or abnormality; or clinically important laboratory tests or haematological abnormalities. Individuals were also excluded if they had clinically manifest dysphagia, defined as a Swallowing Disturbance Questionnaire (SDQ) score of 11 or higher, unless they also had a score of 2 or lower on item 13 (dysphagia) of the Clinical Rating Scale for Progressive Supranuclear Palsy.

Individuals who took any of the following medications within 30 days before baseline were not allowed to enter the study: antipsychotics or other dopamine receptor blockers; CYP3A4 inducers; dopamine agonists and precursors; or monoamine oxidase inhibitors. These medications were also prohibited during the study. Individuals who had been or were currently receiving treatment with a VMAT2 inhibitor were not allowed to enter the study.

Randomisation and masking

The study medical monitor reviewed the screening data of each individual and authorised advancement to the baseline (day –1) visit. After reviewing the screening and baseline criteria, site investigators authorised eligibility for study participation. A member of the site personnel then entered the individual's information into an interactive web response system (IWRS) that was maintained by an external vendor (Signant Health; Blue Bell, PA, USA). The IWRS generated an identification code for each participant and randomly assigned them (1:1) to valbenazine or placebo with no stratification or minimisation. All participants, investigators, study site personnel, and the sponsor (Neurocrine Biosciences) were masked to treatment assignments, with valbenazine or placebo provided in capsules that were identical in appearance (manufactured by Mayne Pharma; Raleigh, NC, USA).

Procedures

Valbenazine dosing was initiated at 40 mg for 2 weeks, self-administered as two capsules (20 mg each) once daily, with or without food. Participants were not required to take their capsules at any particular time of day; however, they were encouraged to take the capsules at the same time each day. If the current dose was well tolerated per investigator judgment, dose increases in 20-mg increments were allowed at the end of weeks 2, 4, and 6 to a target dose of 80 mg per day. Doses could be decreased at any time during the dose-adjustment period (baseline to week 8) for tolerability reasons (per investigator judgment), and multiple dose decreases were allowed. Participants who had a dose decrease could have their dose re-escalated during the dose-adjustment period if the investigator deemed an increase was warranted. During the maintenance period (weeks 9 to 12), further dose escalation was not allowed; however, a participant's dosage could be reduced once (by 20 mg) if not tolerated. A follow-up visit was performed 2 weeks after participants took their final dose of study drug (week 14).

All allowed concomitant medications (prescription, non-prescription, and supplements) that were taken by the participant at any point during the 30 days before

study baseline or at any point during the study were recorded by the investigator. All coexistent diseases or conditions were treated in accordance with prevailing medical practice. Benzodiazepines and opiates were required to be at a stable dose (ie, no as-needed use) for 2 weeks before baseline. Antidepressant therapies were required to be at stable dose for 8 weeks before baseline.

Descriptions (with references) of all KINECT-HD study assessments can be found in the appendix (pp 8–12). Data were collected at study sites and entered into an electronic data system (TrialMaster EDC5.0; Anju Life Sciences; Fort Lauderdale, FL, USA). Assessments were performed at the screening visit (week –4) and baseline visit (day –1), during treatment (week 2, week 4, week 6, week 8, week 10, and week 12), and at follow-up (week 14). The study protocol was revised to allow for remote visits if the participant was unable to attend an in-person visit because of the COVID-19 pandemic. Remote visits were done per judgment of the investigator and in consultation with the study medical monitor. On-site assessments were required for screening, baseline, and study visits at week 10 and week 12. An on-site visit at week 14 was also required for participants who planned to enter the KINECT-HD2 extension study (NCT04400331).

Outcomes

The primary efficacy endpoint was change in the UHDRS TMC from the screening and baseline period (average of the screening and baseline assessments) to the maintenance period (average of the week 10 and week 12 assessments), as scored by on-site study investigators.

Secondary endpoints were: the Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) response status at week 12, defined as a score of 1 (very much improved) or 2 (much improved); mean change from baseline to week 12 in the short-form Quality of Life in Neurological Disorders (Neuro-QoL) Upper Extremity Function T-score; and mean change from baseline to week 12 in the short-form Neuro-QoL Lower Extremity Function T-score.[5]

13 analyses were prespecified as exploratory endpoints (appendix p 1) in the statistical analysis plan. The study also included three prespecified sensitivity analyses for the primary endpoint, two prespecified sensitivity analyses for the secondary CGI-C and PGI-C endpoints (one analysis for each endpoint), and prespecified subgroup analyses on the basis of age, sex, race, baseline CGI-S categories, and baseline PGI-S categories (appendix pp 5–6). Primary and secondary assessments (UHDRS TMC, CGI-C, PGI-C, and Neuro-QoL assessments) at the week 14 follow-up visit (2 weeks after final study dose) were analysed post hoc (appendix p 7). An exploratory wearable-sensor substudy was also prespecified, but the results of that substudy will be presented in a future publication.

Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms, and laboratory tests. Additional safety analyses included mean changes from baseline to week 12 in HADS anxiety and depression scores, Barnes Akathisia Rating Scale (BARS) global and total scores, shifts from baseline in C-SSRS suicidal ideation scores, and parkinsonism severity as quantified by items (retropulsion pull test, finger taps, pronation/supination of hands, arm rigidity, and body bradykinesia) from the UHDRS motor assessment.

Statistical analysis

To calculate sample size and power estimates, nQuery Advisor (version 8) software was used. This program showed that an initial sample size estimate of 112 participants (56 per treatment group) would provide more than 95% power to detect a difference between the valbenazine and placebo treatment groups in the primary endpoint, using a two-sample t-test with a two-sided type 1 error of 0·05. This assumed a mean difference of 2·4 for the UHDRS TMC, with a common SD of 3·3. To account for a potential discontinuation of up to four (7%) participants per treatment group, the target sample size was increased to 120 participants (60 per treatment group). Statistical calculations and summaries were generated using SAS software version 9.4 or later.

Efficacy analyses were performed in the full-analysis set, defined as all randomly assigned participants who received at least one dose of study drug and had at least one evaluable UHDRS TMC change from baseline score during the 12-week, double-blind treatment period. The primary TMC endpoint (ie, mean change from the screening and baseline period to the maintenance period) was analysed using a mixed-effect model for repeated measures with the screening and baseline period TMC score as a covariate; treatment group, visit, treatment group-by-visit interaction, and baseline-by-visit interaction as fixed effects; and participant as a random effect. Results for the primary endpoint are presented as least-squares mean changes by treatment group with standard error of the mean, along with the 95% CI and two-sided p value for the least-squares mean difference between treatment groups. The CGI-C and PGI-C secondary endpoints (ie, response at week 12) were analysed using Fisher's exact test. Results for these endpoints are presented as number and proportion of study participants meeting the response threshold, along with p values for treatment group comparisons that were controlled for multiple comparisons. The Neuro-QoL secondary endpoints (ie, mean changes from baseline to week 12) were analysed with the approach of mixed-effect model for repeated measures used for the primary endpoint.

A fixed-sequence testing procedure was used to control the family-wise error rate for the primary and secondary

endpoints. Testing of hypotheses at each step of the procedure commenced only if all null hypotheses of the previous steps were rejected. The fixed-sequence testing procedure consisted of doing the hypothesis tests for the primary endpoint (UHDRS TMC change from screening and baseline to week 10 and 12), followed by the secondary endpoints in the following prespecified order: CGI-C response at week 12, PGI-C response at week 12, Neuro-QoL Upper Extremity Function T-score change from baseline to week 12, and Neuro-QoL Lower Extremity Function T-score change from baseline to week 12. Each step in the sequential testing procedure used a local two-sided 0·05 level of significance for the null hypothesis being tested.

Statistical analyses for the prespecified exploratory endpoints are presented with the results in the appendix (pp 1–4). Safety analyses were performed in the safety-analysis set, defined as all randomly assigned participants who received at least one dose of study drug and had any available safety data after baseline. As specified in the statistical analysis plan, all safety outcomes were analysed descriptively on the basis of observed cases, with no imputation of missing values, formal hypothesis testing, or designation of primary or secondary safety endpoints.

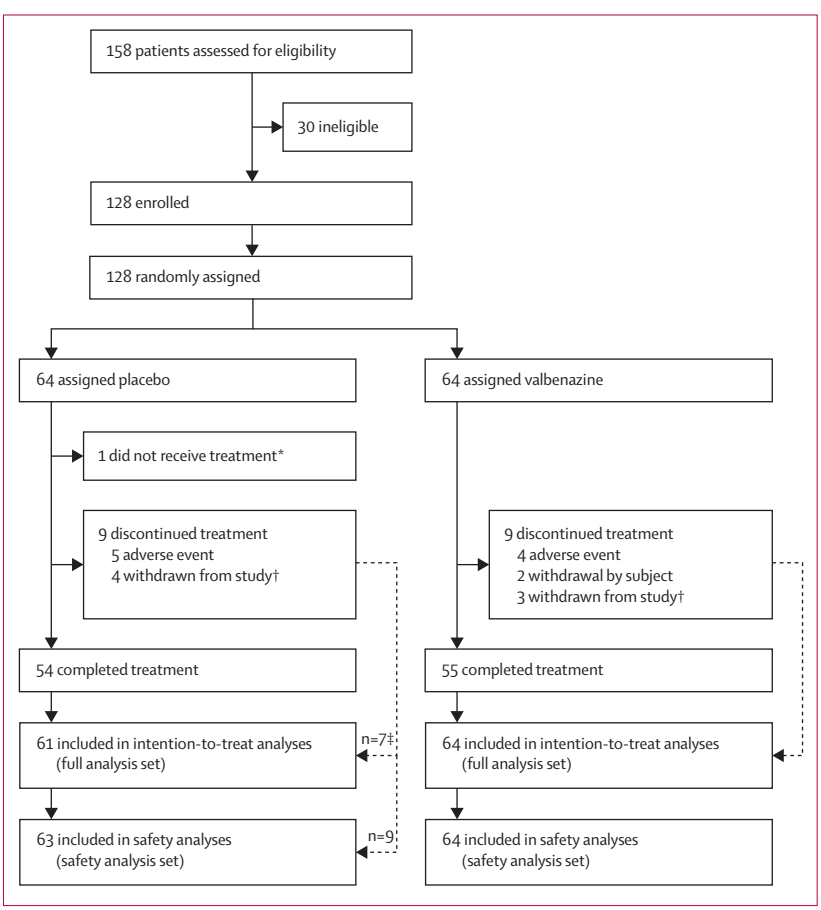

Figure 1: **CONSORT diagram**
*Participant was excluded from intention-to-treat and safety analyses. †Withdrawn from the study because of closure of study site during the study pause because of COVID-19. ‡Two participants in the placebo group who did not have a Unified Huntington's Disease Rating Scale Total Maximal Chorea score at baseline or after baseline were included in the safety analyses but excluded from intention-to-treat analyses.

Role of the funding source

The study sponsor provided study medications and study oversight, analysed the data, and supported professional medical writing services for this Article. The funder of the study was involved in study design, but was not involved in data collection. All data were analysed by the funder after database lock and confirmed by an independent biostatistician of the HSG Steering Committee. Authors affiliated with the study funder contributed to the interpretation of the data.

Results

The screening and double-blind phases of the trial were performed between Nov 13, 2019, and Oct 26, 2021. Of the 158 participants screened for eligibility, 128 were enrolled and randomly assigned (64 to valbenazine, 64 to placebo; figure 1). The full-analysis set included 125 participants (64 assigned to valbenazine, 61 assigned to placebo) and the safety-analysis set included 127 participants (64 assigned to valbenazine, 63 assigned to placebo). 14 (11%) participants in the safety-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)

Data are mean (SD) or n (%). CGI-S=Clinical Global Impression of Severity. MoCA=Montreal Cognitive Assessment. PGI-S=Patient Global Impression of Severity. SDQ=Swallowing Disturbance Questionnaire. TMC=Total Maximal Chorea. UHDRS=Unified Huntington's Disease Rating Scale. *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.

Table 1: **Baseline demographics and disease characteristics in the full-analysis set**

had at least one dose reduction during the double-blind treatment period (11 receiving valbenazine, 3 receiving placebo). The majority of valbenazine dose reductions (six participants) occurred in the 2 weeks before the week 8 visit (end of dose-adjustment period). At all other study visits, two or fewer participants in each treatment group had a dose reduction. All participants in the valbenazine group who had a TEAE leading to dose reduction completed the study.

Of 128 participants randomly assigned to treatment, 111 (87%) reached the final visit of the maintenance period at week 12 (57 in the valbenazine group, 54 in the placebo group). 109 (85%) completed study treatment (55 receiving valbenazine, 54 receiving placebo; figure 1). The most common reason for discontinuing treatment was adverse event (four receiving valbenazine, five receiving placebo). During a pause in study from March 15, to July 1, 2020 because of COVID-19, seven participants (three receiving valbenazine, four receiving placebo) were withdrawn by the study sponsor because of study site closures. 18 participants discontinued study treatment (nine receiving valbenazine, nine receiving placebo).

14 participants (six receiving valbenazine, eight receiving placebo) had one or more important protocol deviations. The most commonly reported deviations were missing assessments because of COVID-19 travel restrictions. Additional information regarding the effects of COVID-19 on study outcomes are provided in the appendix (p 16). The second most common type of deviation was related to study treatment administration or treatment compliance. One participant started taking prescription valbenazine before the week 14 visit and therefore did not discontinue treatment from week 12 to week 14; another participant in the placebo group was enrolled despite meeting two criteria for exclusion. Other violations included deviations in assessment collection caused by rescheduling of on-site visit due to participant or investigator unavailability, refusal by participant to complete the assessment, and randomisation error. None of these protocol deviations were considered to have affected the results or outcome of the study.

Baseline demographics (per participant self-report) and disease characteristics (per investigator assessment) of the full-analysis set were similar between treatment groups (table 1). In the full-analysis set (n=125), 68 (54%) participants were female, 120 (96%) were White, and 117 (94%) were not Hispanic or Latino; mean age (SD) was 53·7 (10·8) years. Mean CAG repeat length of the expanded allele was 43·4 (3·2), and mean UHDRS TMC score at the screening and baseline period was 12·2 (2·6). 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. Mean SDQ total score was 5·0 (6·2) and mean Montreal Cognitive Assessment Score was 23·5 (3·9), with both scores being similar between treatment groups. 92 (74%) participants did not meet the threshold for

	Direction of favourable effect	Placebo			Valbenazine			Treatment difference‡	p value
		Baseline*†	Maintenance period or week 12*†	Change from baseline‡	Baseline*†	Maintenance period or week 12*†	Change from baseline‡		
Primary and secondary efficacy measures									
UHDRS TMC	Negative	12·1 (0·4)	10·6 (0·5)	−1·4 (−2·3 to −0·6)	12·2 (0·3)	7·5 (0·6)	−4·6 (−5·4 to −3·8)	−3·2 (−4·4 to −2·0)	<0·0001
CGI-C response§	Positive	NA	7 (13%)	NA	NA	24 (43%)	NA	30 (11 to 45)	0·0007
PGI-C response§	Positive	NA	14 (26%)	NA	NA	29 (53%)	NA	26 (6 to 44)	0·0062
Neuro-QoL UEF T-score	Positive	47·0 (8·2)	43·9 (9·6)	−3·0 (−5·1 to −1·0)	44·5 (9·0)	43·8 (10·0)	−1·6 (−3·6 to 0·4)	1·4 (−1·5 to 4·3)	0·3304
Neuro-QoL LEF T-score	Positive	48·4 (7·7)	49·1 (8·0)	0·6 (−1·1 to 2·3)	48·1 (8·9)	48·5 (9·5)	−0·3 (−1·9 to 1·4)	−0·9 (−3·2 to 1·4)	NA¶
Key safety measures									
HADS anxiety	Negative	5·4 (4·2)	4·3 (4·1)	−1·4 (NA)	4·0 (4·0)	2·8 (4·1)	−0·9 (NA)	NA	NA
HADS depression	Negative	3·6 (3·3)	3·2 (3·3)	−0·4 (NA)	3·0 (2·6)	2·8 (3·6)	−0·2 (NA)	NA	NA
BARS global	Negative	0·8 (1·0)	0·4 (0·8)	−0·5 (NA)	0·5 (0·9)	0·3 (0·6)	−0·2 (NA)	NA	NA
BARS total	Negative	1·6 (1·8)	1·0 (1·4)	−0·6 (NA)	1·1 (1·5)	0·8 (1·3)	−0·3 (NA)	NA	NA
UHDRS parkinsonism	Negative	7·5 (3·7)	6·4 (3·9)	−1·0 (NA)	8·6 (4·4)	8·2 (4·5)	−0·3 (NA)	NA	NA

Data are n (%), mean (SEM), mean change (95% CI), or mean treatment difference. BARS=Barnes Akathisia Rating Scale. CGI-C=Clinical Global Impression of Change. HADS=Hospital Anxiety and Depression Scale. LEF=Lower Extremity Function. NA=not applicable. Neuro-QoL=Quality of Life in Neurological Disorders. PGI-C=Patient Global Impression of Change. SEM=standard error of the mean. TMC=Total Maximal Chorea. UEF=Upper Extremity Function. UHDRS=Unified Huntington's Disease Rating Scale. *Mean (SEM) for the screening and baseline period (average of values from screening and baseline of each participant) and the maintenance period (average of values from week 10 and week 12 for each participant) are presented for UHDRS TMC (primary endpoint). †Mean (SD) at study baseline (day −1) and week 12 are presented for Neuro-QoL UEF and LEF (secondary endpoints) and for HADS, BARS, and UHDRS parkinsonism. ‡Least-squares mean changes and differences are presented for UHDRS TMC and Neuro-QoL. Mean changes are presented for HADS, BARS, and UHDRS parkinsonism. §CGI-C and PGI-C response status (secondary endpoints) was defined as the percentage of participants who had a rating of much improved or very much improved at week 12. ¶Not applicable because the previous endpoint in the prespecified fixed-sequence testing procedure (Neuro-QoL UEF T-score) was not statistically significant.

Table 2: **Primary, secondary, and key safety measures**

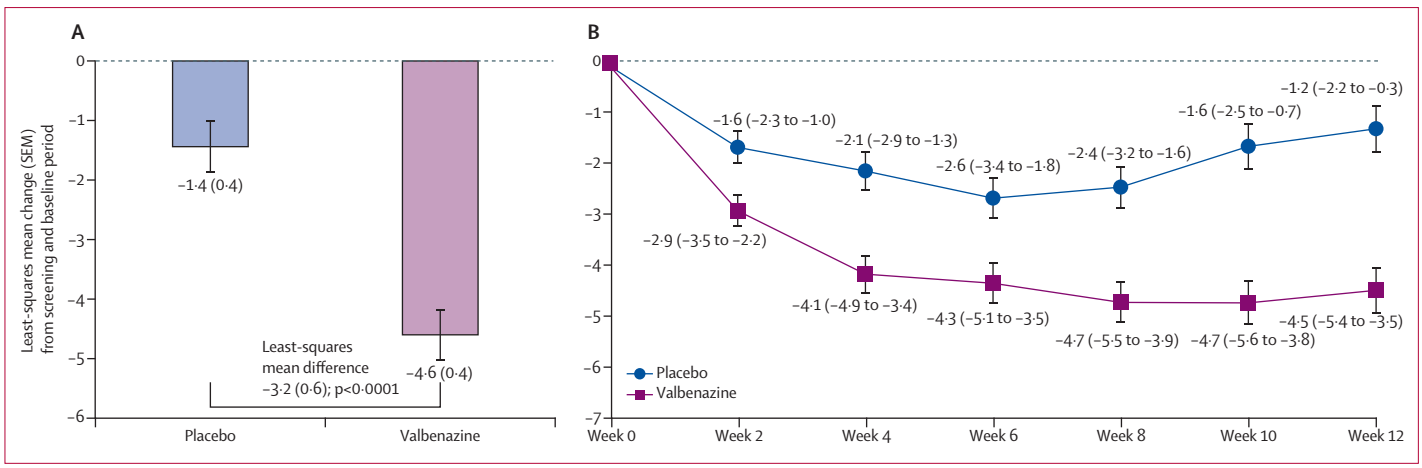

Figure 2: **Mean changes in the UHDRS Total Maximal Chorea score**

Mean changes in the UHDRS Total Maximal Chorea score from the screening and baseline period to the maintenance period (primary endpoint; A) and at visits after baseline (exploratory endpoint; B). 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 visits. Error bars represent SEMs; numbers in parentheses represent 95% CIs. SEM=standard error of the mean. UHDRS=Unified Huntington's Disease Rating Scale.

anosognosia, defined as a six points or greater difference between patient and clinician scores on the Anosognosia Scale (appendix p 3).[18]

The study met its primary endpoint with a statistically significant reduction in chorea severity for valbenazine versus placebo as indicated by changes in UHDRS TMC score, on the basis of assessments by on-site study investigators (table 2; figure 2). Least-squares mean changes (SEM) from the screening and baseline period (based on the average of screening and baseline values of each participant) to the maintenance period (based on the average of week 10 and week 12 values of each participant) were greater for valbenazine than for placebo (–4·6 *vs* –1·4; difference –3·2 [0·6], 95% CI –4·4 to –2·0; p<0·0001).

The study also met the secondary CGI-C and PGI-C endpoints, with statistically significant differences in response status (ie, score of 1 indicating very much improved or 2 indicating much improved) between treatment groups at week 12 (table 2; figure 3). However, the change from baseline to week 12 was not statistically significant for Neuro-QoL Upper Extremity Function T-score (table 2; figure 3); statistical analysis for Lower Extremity Function was not done per the fixed-sequence testing procedure. Results for the prespecified exploratory endpoints, sensitivity analyses, and subgroup analyses are presented in the appendix (pp 2–6), along with the results from the post-hoc follow-up (week 14) analyses (appendix p 7). The prespecified exploratory endpoint of UHDRS TMC mean changes over time are graphically presented (figure 2B) because these provide context for understanding improvement over time for the primary efficacy assessment.

Valbenazine was generally well tolerated. Of the 55 participants who were treated with valbenazine at the week 12 visit, 45 (82%) were taking 80 mg, seven (13%) were taking 60 mg, two (4%) were taking 40 mg, and one (2%) was taking 20 mg. In the safety-analysis set, the most commonly reported TEAEs with valbenazine were somnolence, fatigue, and falls; however, the placebo group had a similar incidence of falls (table 3). Nine (14%) participants in the valbenazine group had a dose reduction because of TEAEs, most commonly for fatigue (n=4) or somnolence (n=3). More than 5% of participants treated with valbenazine reported urticaria (9%) and rash (8%).

Discontinuation of study drug because of TEAEs was similar between treatment groups (table 3). Three participants had urticaria that resulted in valbenazine discontinuation; all three cases resolved within 1 week of discontinuation. All other TEAEs that led to treatment discontinuation occurred in one participant each. Two participants in the placebo group had a serious TEAE: one with colon cancer (withdrawn from study and subsequently died) and one with psychosis (withdrawn from study). The valbenazine group had one serious TEAE of angioedema in a participant who had known allergy to shellfish and sodium benzoate. Because the participant reported consuming shellfish with sodium benzoate preservative 1 day before experiencing angioedema, the investigator judged this event as being unlikely to be related to study treatment. The angioedema resolved after appropriate emergency treatment, and there was no change in study drug dose or withdrawal from the study.

Mean changes from baseline to week 12 in additional safety scales were similar between treatment groups (table 2). These results indicated 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 behaviour with valbenazine, with no participants reporting suicidal ideation as a TEAE and no participants

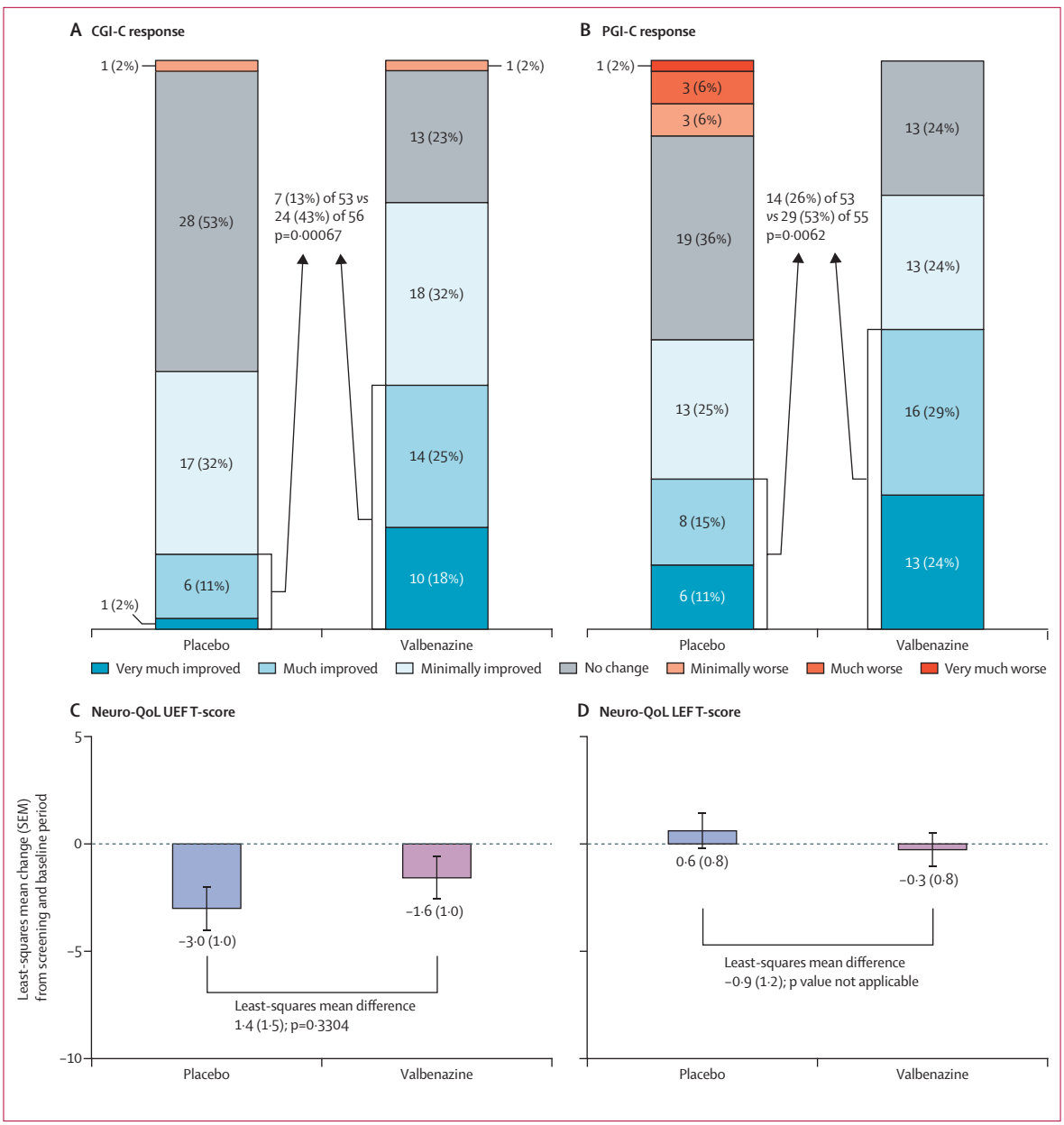

***Figure 3*: CGI-C and PGI-C response status at week 12 and mean changes from baseline to week 12 in Neuro-QoL T-scores for UEF and LEF (secondary endpoints)**

For the distribution of CGI-C scores (A) and PGI-C scores (B) by treatment group, brackets indicate the percentage and number of participants who met the threshold for a good clinical response, defined as a rating of much improved or very much improved from baseline. Per the prespecified fixed-sequence testing procedure, the p value for the Neuro-QoL UEF endpoint (C) is presented because the CGI-C and PGI-C endpoints reached statistical significance. No p value was provided for the Neuro-QoL LEF endpoint (D) because the UEF endpoint did not reach statistical significance. CGI-C=Clinical Global Impression of Change. LEF=Lower Extremity Function. Neuro-QoL=Quality of Life in Neurological Disorders. PGI-C=Patient Global Impression of Change. UEF=Upper Extremity Function.

having an increase in suicidal ideation or any suicidal behaviour 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 (mm Hg) were small in both treatment groups, for both systolic blood pressure (valbenazine, –1·8 [15·9]; placebo, –0·8 [11·7]) and diastolic blood pressure (valbenazine, 0·8 [12·1]; placebo, –2·5 [10·5]).

Discussion

Treatment with valbenazine at doses of up to 80 mg once per day significantly improved chorea, as demonstrated by the mean change in UHDRS TMC scores from the screening and baseline period to the maintenance period

	Placebo (n=63)	Valbenazine (n=64)
Summary		
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.

Table 3: **Treatment-emergent adverse events in the safety-analysis set**

on the basis of evaluations from on-site study investigators, with no statistical difference between men and women. The effects of valbenazine on chorea were seen as early as week 2, as participants completed the first dose level (40 mg), with consistently greater improvements relative to placebo at all subsequent visits (week 4 to week 12; appendix p 1). Improvements in UHDRS TMC score were supported by CGI-C and PGI-C response status at week 12 (secondary endpoints). However, no statistical difference between treatment groups was found in the secondary NeuroQoL Upper Extremity Function endpoint, and no statistical analysis was performed for the Lower Extremity Function endpoint per the fixed-sequence testing procedure.

These primary and secondary endpoint results were similar to the reductions in chorea and global improvements with other VMAT2 inhibitors (tetrabenazine and deutetrabenazine), as reported in phase 3 trials.[9,10] Per protocol, valbenazine dosing was increased to a maximum dose of 80 mg per day; however, doses could be decreased if intolerable side-effects occurred. The UHDRS TMC, CGI-C, and PGI-C results indicated that the once-per-day dosing regimen was effective, demonstrating that improvements were noticeable to both clinicians and participants. Moreover, valbenazine was well tolerated, with 45 (82%) of 55 participants treated with valbenazine taking 80 mg at end of treatment (week 12).

KINECT-HD is, to our knowledge, the first phase 3 study in Huntington's disease to implement the Neuro-QoL, Huntington's Disease Health Index (HD-HI),[16] and Anosognosia Scale[17,18] as outcome measures. The Neuro-QoL was used to assess physical function, but statistical significance was not reached (Upper Extremity Function) or not evaluated because of the fixed-sequence testing procedure (Lower Extremity Function). Most participants had scores that 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. The HD-HI results indicated greater reductions with valbenazine relative to placebo in patient-reported disease burden related to mobility, abnormal movements, and hand and arm function. This instrument was developed using input from individuals with Huntington's disease to reflect the physical, mental, and social issues that have the greatest impact for them and their caregivers. Validation and testing of the HD-HI has demonstrated high internal consistency and reliability.[16]

Anosognosia is common in Huntington's disease[19] and can affect an individual's ability to reliably recognise the severity and impact of their symptoms. The Anosognosia Scale was employed to evaluate the presence of anosognosia, which could have undermined the reliability of patient-reported outcomes used as study endpoints. Interestingly, 74% of participants in KINECT-HD did not demonstrate anosognosia at baseline, as indicated by strong agreement between patient and clinical ratings of symptoms and functional capabilities (less than a 6-point difference in patient-rated and clinician-rated scores), nor was there any notable change in anosognosia during the study. These results indicate that anosognosia was not likely to be a factor in the interpretation of outcomes in this study.

TEAEs that affected more than 10% of patients treated with valbenazine were somnolence, fatigue, and falls. Somnolence is a known side-effect of valbenazine, and practical approaches for managing somnolence can include reducing the dose and recommending that patients take their dose in the evening or before bedtime. The incidence of falls was the same between the placebo and valbenazine groups, which is consistent with the known risk of falls in Huntington's disease.[20] 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.[15] There was no evidence

of treatment-emergent suicidal behaviour 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,[21] all patients taking a VMAT2 inhibitor or other medication for chorea should be monitored regularly for suicidal thoughts and behaviours.

COVID-19 safer-at-home orders resulted in a pause in study enrolment and activity from March 15, 2020, to July 1, 2020, as agreed upon by the study sponsor and the HSG. The pause resulted in an amendment to the study protocol that allowed for remote assessments for selected study visits. However, upon study resumption few deviations to the protocol were attributed to COVID-19, and none of these changes was found to affect the overall study outcome (appendix p 16). Participants who were withdrawn because of the COVID-19 pandemic were allowed to enter the currently ongoing open-label extension study (KINECT-HD2 [NCT04400331]).

Potential limitations of KINECT-HD include the short study duration and prohibition of antipsychotics. Because individuals with chorea are likely to require treatment for years, the short study duration is not sufficient to detect long-term efficacy and safety. However, longer-term follow-up will be addressed by KINECT-HD2. Monotherapy with either a VMAT2 inhibitor or antipsychotic is generally preferred; however, some individuals require dual therapy because of intractable chorea, neuropsychiatric symptoms, or both. Therefore, the prohibition of antipsychotics during the double-blind, placebo-controlled phase might not reflect real-world treatment patterns in Huntington's disease. The use of concomitant antipsychotics with valbenazine treatment will be further evaluated in KINECT-HD2.

The strengths of KINECT-HD include the robust design (randomised, double-blind, and placebo-controlled), relatively large sample size (ie, it was well powered), and use of a standard primary outcome measure (UHDRS TMC score). The secondary and exploratory efficacy and broad safety assessments were selected to provide a comprehensive understanding of the effects of valbenazine beyond motor control, including maintenance of psychiatric stability and impacts on physical, mental, emotional, and social functioning and quality of life, as well as its safety and tolerability in individuals with Huntington's disease. However, without head-to-head trials, no inferences can be drawn on the relative efficacy and safety of valbenazine relative to other medications used to treat chorea.

The results of KINECT-HD support the efficacy of valbenazine in individuals with chorea associated with Huntington's disease. Although chorea is only one of the many symptoms experienced by individuals with Huntington's disease, it is treatable. Early detection of chorea, assessment of its impact on physical, mental, emotional, and social functioning, and evaluation of the need for treatment might decrease burden and improve outcomes in individuals living with this devastating neurodegenerative disease.

Contributors

EFS, DOC, EK, JG, RM, HZ, GSL, and DH were involved in study concept, study design, and statistical analysis. EFS, DOC, EK, JG, and all Huntington Study Group (HSG) KINECT-HD collaborators participated in some of the data acquisition, study management (coordination, monitoring, and oversight), and interpretation of study results. HZ and EFS verified the data. Per HSG requirements for publication, Christopher Beck from the University of Rochester (HSG collaborator [Steering Committee] and independent HSG statistician) also verified the data. EFS, DOC, EK, JG, RM, HZ, GSL, and DH all had full access to the data, reviewed manuscript drafts, provided critical feedback on the drafts with interpretation of the data, and approved the final draft for submission. All authors and study group collaborators were able to access the full data if they wished to do so.

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Declaration of interests
EFS has received honoraria as an advisory board member, consulted for, received research funding from, and served on the speakers' bureau for Cures Within Reach, the Cure Huntington's Disease Initiative, Huntington's Disease Society of America, Neurocrine Biosciences, Prilenia, Roche/Genentech, UniQure, Novartis, Teva Pharmaceuticals, Vaccinex, and Sunovion. DOC has received research funding from Vaccinex, the Cure Huntington's Disease Initiative, Huntington's Disease Society of America, Griffin Foundation, Genentech, Wave Life Sciences, Neurocrine Biosciences, Teva Pharmaceuticals, AbbVie, and Biogen. DOC has also served as a consultant to Neurocrine Biosciences, Wave Life Science, Teva Pharmaceuticals, Acadia, Alterity, Genentech/Roche, and Lundbeck. RM served as a consultant for Global Kinetic Corporation and was on the speaker bureau for Teva Pharmaceuticals, Adamas Pharmaceuticals, Kyowa Kirin, Sunovion, and Accorda Therapeutics. DOC has received research grants from Prilenia, Global Kinetic Corporation, Northera, Neurocrine Biosciences, and Cerevel. EK and JG have no conflicts to disclose. HZ, GSL, and DH are full-time employees of Neurocrine Biosciences and own stock in the company.

Data sharing
Data will not be publicly available, but requests to the study sponsor (Neurocrine Biosciences) and the Huntington Study Group (HSG) will be considered if the proposal is methodologically sound and ethically appropriate per HSG publication policies. Each request will be reviewed by both the study sponsor and HSG on a case-by-case basis. Individuals or institutions who would like access to the data should contact the study sponsor.

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