Valbenazine in Huntington's Disease Chorea

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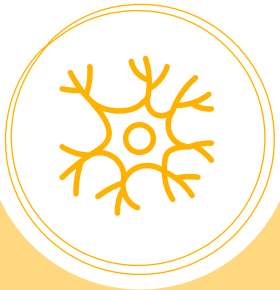
HD, Huntington's disease.

Overview of HD

HD is a Hereditary Neurodegenerative Disorder[1,2]



Characterized by a **progressive neurodegeneration** in the **cortex and striatum**

Inherited in an **autosomal-dominant** manner

HTT gene

Typically diagnosed between **30-50 years**[2,3]

Triad of symptoms: motor, cognitive, and psychiatric

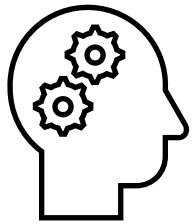
Currently no cure; treatment goals are to manage symptoms and improve QoL

HD, Huntington's disease; HTT, huntingtin; QoL, quality of life.

1. Roos RA. *Orphanet J Rare Dis*. 2010;5:40. 2. Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition*. Huntington's Disease Society of America; 2011. 3. Solberg OK, et al. *J Huntingtons Dis*. 2018;7(1):77-86.

The Triad of Symptoms in HD

Individuals with HD exhibit a wide range of symptoms in 3 key areas:[1,2]



Motor Symptoms

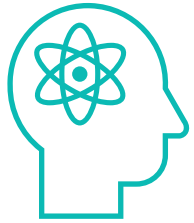
Involuntary movements (chorea) and impaired voluntary movements

Chorea is the most recognized motor symptom in HD, but dystonia, bradykinesia, myoclonus and tremor can also be present

Cognitive Symptoms

Reduced speed and flexibility in mental processing and executive function*

Learning and memory issues begin early in the disease, with subclinical cognitive changes that can occur 15 years before diagnosis



Psychiatric Symptoms

Personality and behavioral changes (depression, irritability, psychosis)

Anxiety, apathy, obsessive compulsive disorder, and agitation may also be present

*Executive functions include high-order cognitive abilities such as working memory, inhibitory control, cognitive flexibility, planning, reasoning, and problem solving.[3] HD, Huntington's disease.

1. Roos RA. *Orphanet J Rare Dis*. 2010;5:40. 2. Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition*. Huntington's Disease Society of America. 2011. 3. Cristofori I, et al. Executive functions. *Handb Clin Neurol*. 2019;163:197-219.

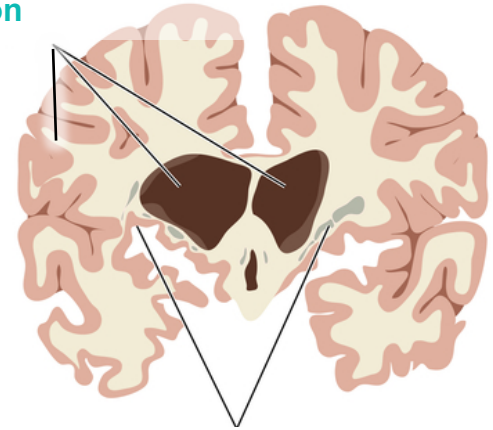
HD Chorea

HD Chorea Mechanism of Disease Video

Dopamine Dysfunction in HD Chorea[1-3]

HD

Degeneration of the cortex contributes to **cognitive deterioration**



Atrophy of the basal ganglia (**striatum**) leads to movement disturbances and eventually progressive global decline

Striatal atrophy

↓

Disruption in **DA, GABA,** and **Glu** pathways

↓

Overstimulation of **DA receptors**

↓

Choreiform movement

HD DA synapse

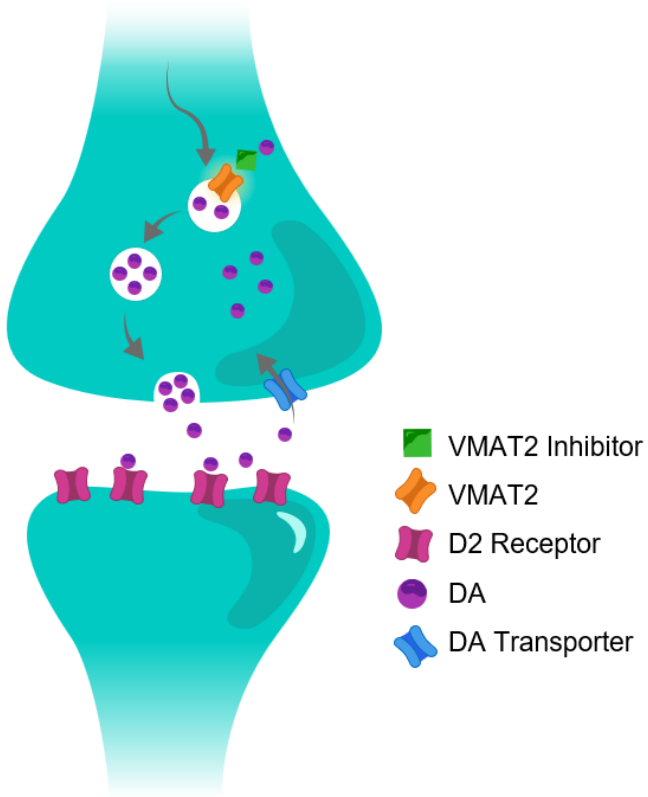


Image courtesy of The Huntington's Disease Association[3]

DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; HD, Huntington's disease; VMAT2, vesicular monoamine transporter 2.

1. Coppen EM, Roos RA. *Drugs*. 2017;77(1):29-46. 2. The European Huntington's Disease Network. Accessed July 7, 2021. http://www.ehdn.org/about-hd/. 3. Huntington's Disease Association. Accessed August 2, 2023. https://www.hda.org.uk/seecmsfile/?id=110

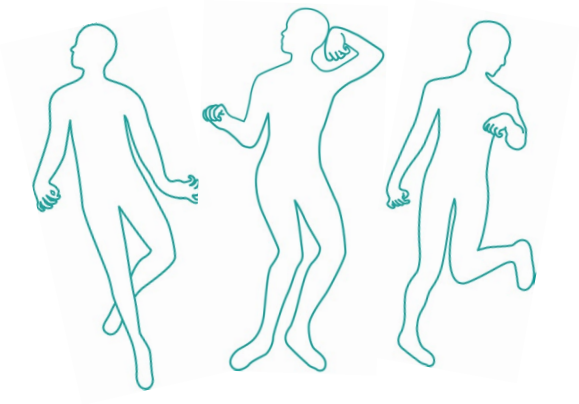
Chorea is a Hallmark Symptom of HD

Approximately **41,000 Americans** have manifest HD, with **>200,000** at risk of inheriting the disease[1,2]

~90% of people with HD experience chorea[3]

Chorea is typically, the symptom leading to **diagnosis of HD**[4]

- Chorea is characterized by sudden, irregular, unpredictable, involuntary movements[4,5]
- Increases in **intensity and affected body regions** over time, starting at the extremities and progressing to the face, neck, shoulder and trunk[3-5]
- The evolution of chorea **varies for each patient**[3]



Face and OBL → **Trunk** → **Extremities** → **Gait**

HD, Huntington's disease; OBL, oral-buccal-lingual.

1. Yohrling G, et al. *Neurology*. 2020;94(15 Supplement). 2. Huntington's Disease Society of America. Accessed March 27, 2023. https://hdsa.org/what-is-hd/overview-of-huntingtons-disease. 3. Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition*. Huntington's Disease Society of America; 2011. 4. Frank S. *Neurotherapeutics*. 2014;11(1):153-160. 3 5. Cubo E, et al. Accessed July 7, 2021. https://www.movementdisorders.org/MDS/About/Movement-Disorder-Overviews/Chorea--Huntingtons-Disease.htm.

Impact of HD Chorea

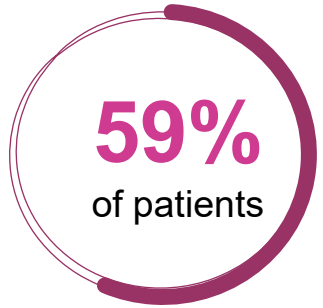
Physical/Functional Impact[1-3]

- Speaking and swallowing
- Walking, frequent falls and injuries
- Getting in and out of bed
- Cooking/eating, taking medication
- Getting dressed/washed
- Using the restroom
- Stop working due to worsening symptoms
- Assistance with daily activities from caregivers

Social/Emotional Impact[1,3,4]

- Anxiety and stress
- Require emotional support from caregivers
- Embarrassment
- Isolation
- Social stigma (often mistaken for drunkenness)

Most patients and caregivers consider **managing chorea as "very important"[1*]**



Top reasons why patients indicated chorea management was important[1*]

- **Loss of independence (18%)**
- **Unpredictability/uncontrollability (18%)**
- **Fear or chorea getting worse (15%)**
- **Fear of falling (15%)**
- **Painful/harmful (15%)**
- **Impact on family life (13%)**

*In a survey assessing the impact of chorea on overall functioning and health-related quality of life; Survey was a 4-point Likert scale; question "How important is it to you to control of manage your chorea?"[1]1. Thorley EM, et al. *Patient.* 2018;11(5):547-559. 2. Simpson JA, et al. *J Huntingtons Dis.* 2016;5(4):395-403. 3. Claassen DO, et al. *J Health Econ Outcomes Res.* 2021;8(1):99-105. 4. Sherman CW. *Neuropsychol Rehabil.* 2020;30(6):1150-1168.

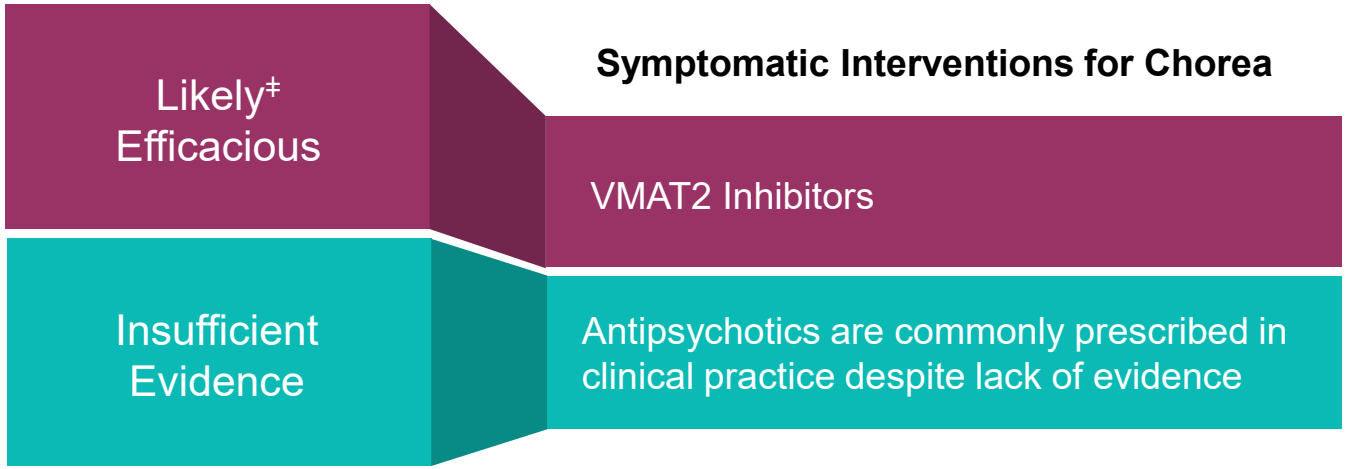
Treatment Guidelines for HD Chorea

- Three VMAT2 inhibitors are FDA approved for chorea associated with HD:
  - **Valbenazine**, a unique, selective VMAT2 inhibitor, approved in 2023[1,4*]
  - **Deutetrabenazine**, a deuterated version of tetrabenazine, approved in 2017[2]
  - **Tetrabenazine**, approved in 2008[3]

Valbenazine was not approved at the time of this analysis, therefore was not included in the review

International Parkinson and Movement Disorder Society (MDS) –

Evidence-Based Review on Treatments in HD 2022[4]



Conclusion[4]:

Data are limited and only support the use of VMAT2 inhibitors for symptomatic treatment of chorea

*From in vitro studies ‡Based on moderate level of evidence; no direct comparisons have been conducted.

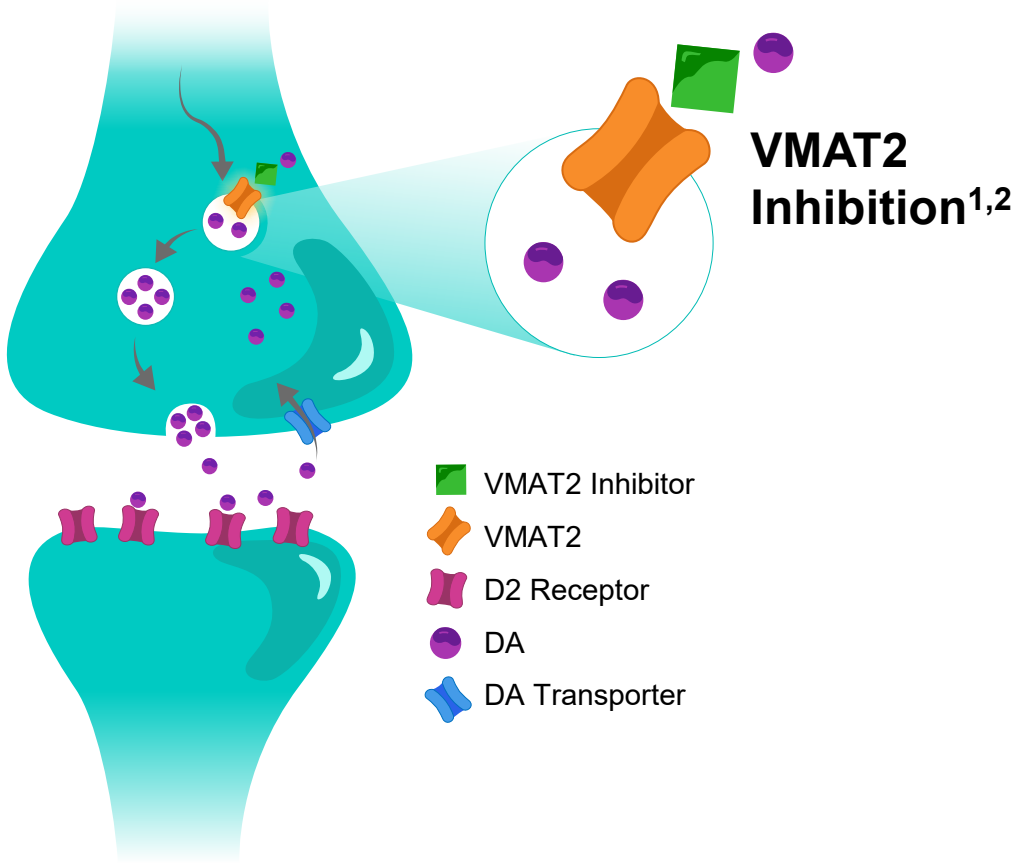
FDA, Food and Drug Administration; HD, Huntington's disease; VMAT2, vesicular monoamine transporter 2.

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.2. AUSTEDO [package Insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.3. XENAZINE [package insert]. Washington, DC: Prestwick Pharmaceuticals Inc
4. Ferreira JJ, et al. A MDS Evidence-Based Review on Treatments for Huntington's Disease. 2022.Movement Disorders. 37(1):25-35. 5. Brar S, et al. Clin Pharmacol Drug Dev. 2023;12(4):447-456.

Overview of Valbenazine

Valbenazine Mechanism of Action

Package Insert



Valbenazine is FDA-approved for the treatment of adults with chorea associated with Huntington's disease[3]

The exact mechanism of action of valbenazine for chorea in HD is unclear

It is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release[3]

Valbenazine Mechanism of Action Video

FDA, Food and Drug Administration; HD, Huntington's disease; VMAT2, vesicular monoamine transporter 2.

1. Coppen EM, Roos RAC. Drugs. 2017:77;29-46. 2. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed July 7, 2021. https://www.ncbi.nlm.nih.gov/books/NBK548187/?report=reader. 3. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

Valbenazine Important Safety information

- **Depression and Suicidality in Patients with Huntington's Disease: VMAT2 inhibitors, including INGREZZA, can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidal ideation, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidal ideation and behavior and instruct them to report behaviors of concern promptly to the treating physician. Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.**

- **CONTRAINDICATIONS:** INGREZZA is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA.

- **WARNINGS & PRECAUTIONS**
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including cases of angioedema involving the larynx, glottis, lips, and eyelids, have been reported in patients after taking the first or subsequent doses of INGREZZA. Angioedema associated with laryngeal edema can be fatal. If any of these reactions occur, discontinue INGREZZA.

TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

Valbenazine Important Safety information Cont.

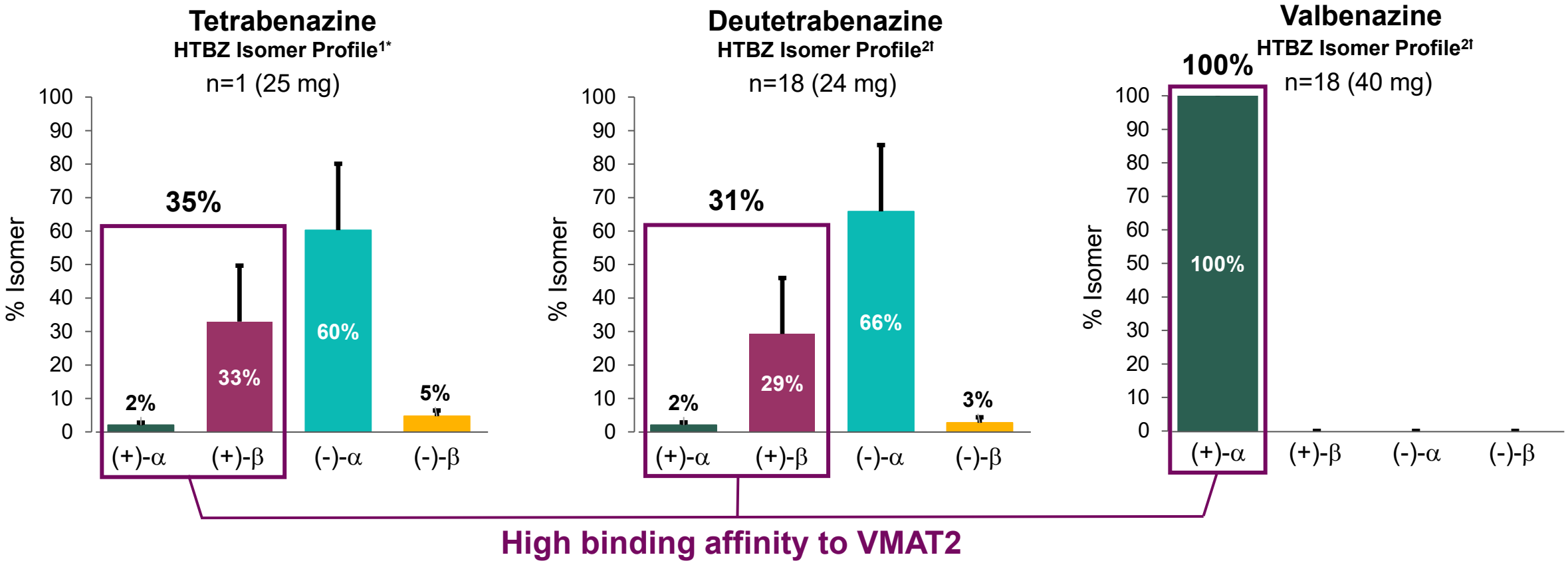
- **Somnolence and Sedation:** INGREZZA can cause somnolence and sedation. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA
- **QT Prolongation:** INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.
- **Neuroleptic Malignant Syndrome:** A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission, including INGREZZA. The management of NMS should include immediate discontinuation of INGREZZA, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If treatment with INGREZZA is needed after recovery from NMS, patients should be monitored for signs of recurrence.
- **Parkinsonism:** INGREZZA may cause parkinsonism. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

Valbenazine Delivers a Unique Metabolite Profile and Pharmacology Inhibiting VMAT2[1]

- (+) isomers have a **high affinity for VMAT2** with no appreciable affinity for off-target receptors (e.g., DA, 5-HT, NE)[1,2]



*Concentrations of HTBZ isomers were determined in a serum sample, from 1 patient taking tetrabenazine 25 mg, that was purchased from a commercial specimen bank. †The pharmacokinetics of valbenazine and its [+]-a-HTBZ metabolite, and each of the 4 deutetrabenazine metabolites, were assessed in 18 male subjects randomized to receive single-dose valbenazine 40 mg and deutetrabenazine 24 mg (two 12 mg tablets). In this phase 1, open-label, crossover study, blood samples were obtained predose and at multiple intervals postdose. Graphs represent % isomer of area under the curve from time 0 to infinity. High binding affinity defined as relatively lower K_i (<1000 nM).

VMAT2, vesicular monoamine transporter 2; HTBZ, dihydrotetrabenazine; K_i, inhibitory constant; nM, nanomolar.

1. Skor H, et al. *Drugs* R D. 2017;17(3):339-359 2. Brar S, et al. *Clin Pharmacol Drug Dev*. 2023 Apr;12(4):447-456.

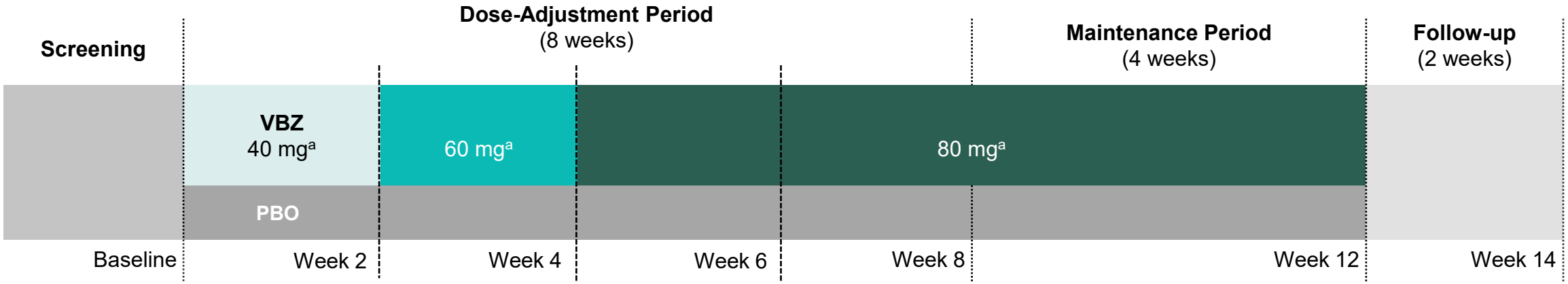
These data do not imply superiority of any compound. Head-to-head trials comparing tetrabenazine, deutetrabenazine, or valbenazine have not been conducted.

KINECT®-HD

Phase 3, Randomized, Double-blind, Placebo-controlled Study of Valbenazine for Chorea in HD

Study Design[1,2]

KINECT®-HD was 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 HD



- **12-week** treatment period
- Final study visit after a 2-week washout

- **128 adult participants**
- Randomized 1:1
- United States/Canada

[a]Doses represent maximum daily doses during each 2-week interval in the dose-adjustment period and during the maintenance period.
FDA, US Food and Drug Administration; HD, Huntington's disease; 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 Identifier: NCT04102579.

ClinicalTrials.gov Identifier: NCT04102579

Eligibility Criteria

Key Inclusion Criteria

- Adults 18 to 75 years old with a clinical diagnosis of HD with chorea
- Expanded CAG repeat (≥37) in HTT
- TMC score ≥8 at screening and baseline
- Total Functional Capacity (TFC) score ≥5 at screening*

Key Exclusion Criteria

- Serious, unstable, untreated, or undertreated medical or psychiatric illness
- HADS depression subscale score ≥11; Significant risk for suicidal ideation or behavior
- Clinically manifest dysphagia, SDQ score ≥11
- Use of antipsychotics or other dopamine receptor blockers, strong CYP3A4 inducers, dopamine agonists/precursors, monoamine oxidase inhibitors, or VMAT2 inhibitors

AV, atrioventricular; CAG, cytosine, adenine, and guanine; HADS, Hospital Anxiety and Depression Scale; HD, Huntington's disease; HTT, huntingtin gene; SDQ, Swallowing Disturbance Questionnaire; TMC, total maximal chorea; UHDRS, Unified Huntington's Disease Rating Scale; VMAT2, vesicular monoamine transporter.
*Score of 5 to 10 required a reliable caregiver to ensure drug administration and attendance at study visits.
Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Outcomes

1 Primary Efficacy Endpoint

Change from **baseline** (average of screening and baseline score) to **maintenance** (average of Weeks 10 and 12) in UHDRS TMC score as assessed by **on-site** study investigators

2 Secondary Efficacy Endpoints

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

! Key Safety Endpoints

AEs, Clinical laboratory tests,
Vital signs, Physical examinations
ECG, HADS, C-SSRS
BARS, UHDRS motor score (items for parkinsonism)

Prespecified Exploratory Endpoints

- TMC Change at Each Visit (screening and baseline period to each postbaseline study visit)
- Central Video Rater Assessments
- CGI-C and PGI-C response statuses* at Weeks 2 through 10
- Huntington's Disease Health Index (HD-HI) at Week 12
- Anosognosia Scale (AS) at Week 12
- Wearable Movement Sensors

AE, adverse event; BARS, Barnes Akathisia Rating Scale; CGI-C, Clinical Global Impression of Change; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; HADS, Hospital Anxiety and Depression Scale; PGI-C, Patient Global Impression of Change; TMC, total maximal chorea; UHDRS, Unified Huntington's Disease Rating Scale. *Participants with CGI-C or PGI-C scores of either a 1 ("very much improved") or a 2 ("much improved") were classified as responders. Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Baseline Demographics

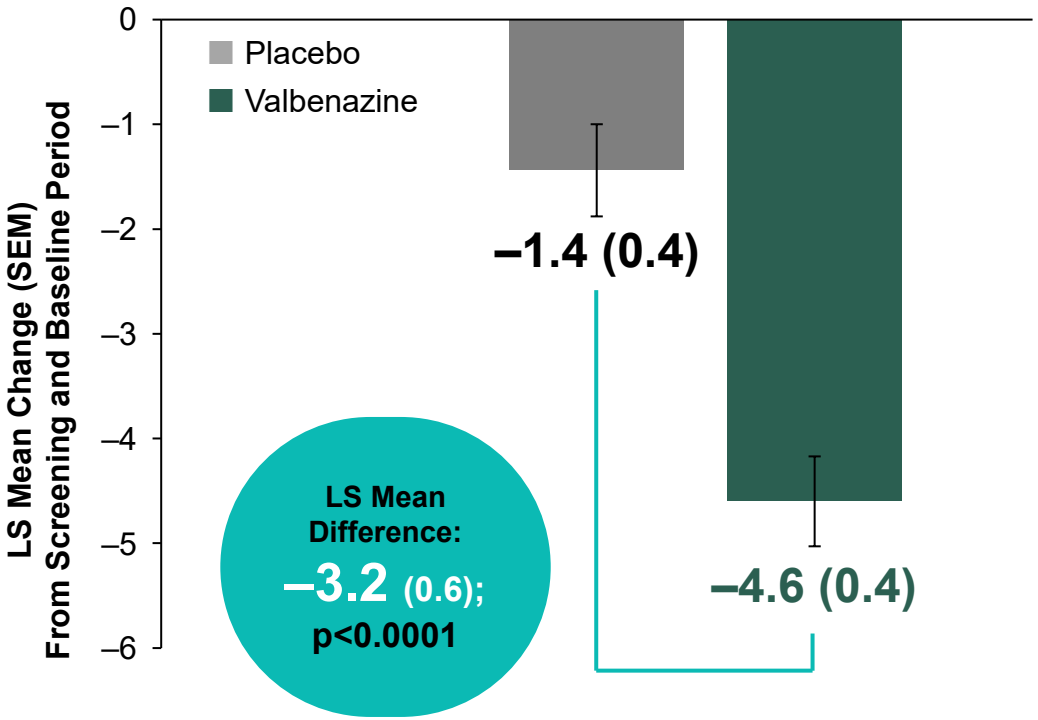
- Baseline demographics were similar between treatment groups
- Almost half of all participants had moderate or severe chorea, with
  - 61 (49%) having a CGI-S score of ≥4
  - 56 (45%) having a PGI-S score of ≥3

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)

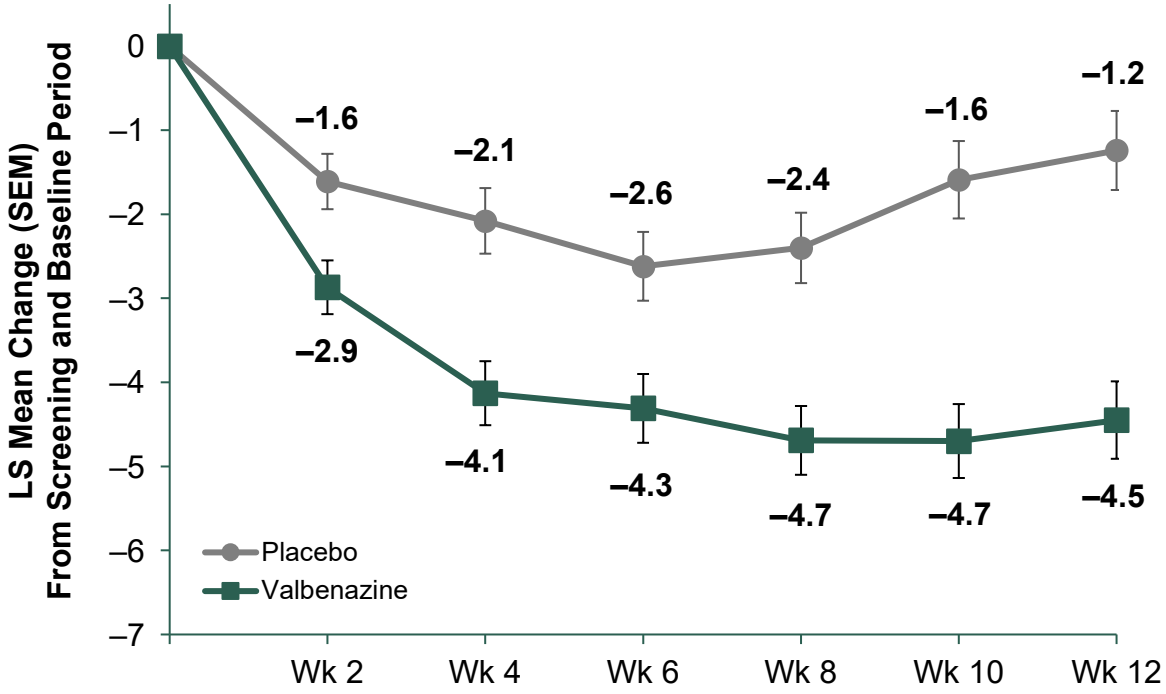
CAG, cytosine, adenine, and guanine; CGI-S, Clinical Global Impression of Severity; MoCA, Montreal Cognitive Assessment; PGI-S, Patient Global Impression of Severity; SD, standard deviation; SDQ, Swallowing Disturbance Questionnaire; TMC, total maximal chorea; UHDRS, Unified Huntington's Disease Rating Scale.
*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.
Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504.

Mean Changes in UHDRS TMC

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



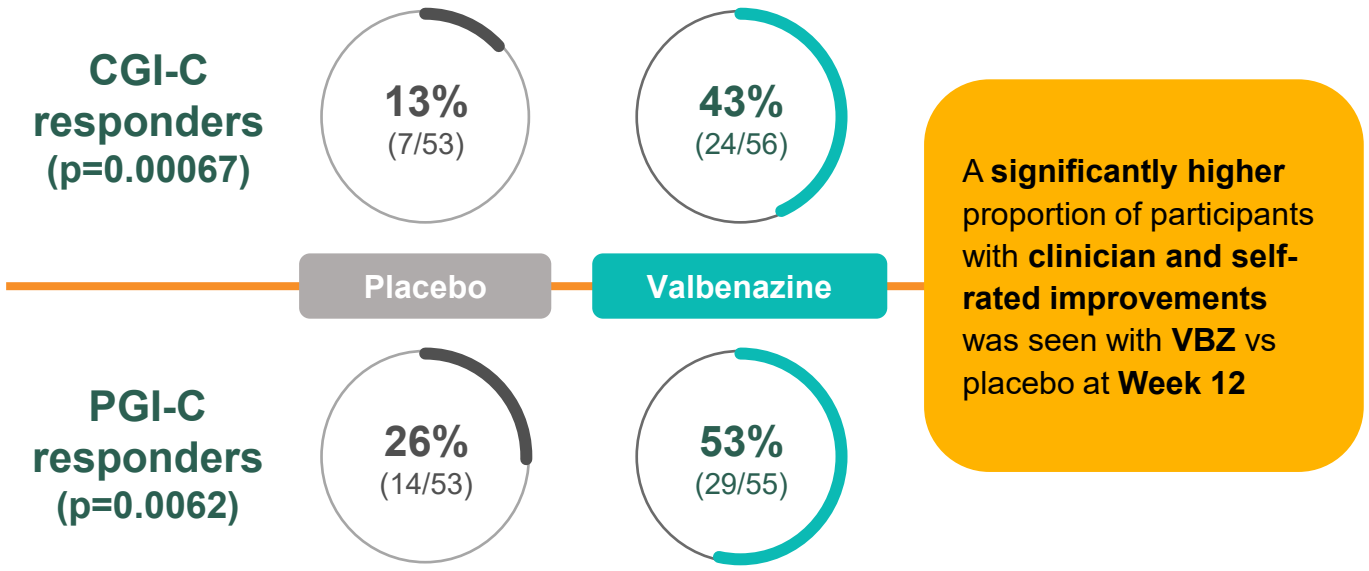
Prespecified Exploratory Endpoint:
UHDRS TMC mean changes over time



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 Weeks 10 and 12. Error bars represent SEMs; numbers in parentheses represent 95% CIs. CI, confidence interval; LS, least squares; SEM, standard error of the mean; UHDRS, Unified Huntington's Disease Rating Scale; TMC, total maximal chorea; Wk, week. Furr Stimming E, et al. *Lancet Neurol*. 2023;22(6):494-504.

Secondary Endpoints

CGI-C and PGI-C Response Status at Week 12



A **significantly higher** proportion of participants with **clinician and self-rated improvements** was seen with **VBZ** vs placebo at **Week 12**

Mean change from baseline to Week 12 in the Neuro-QoL

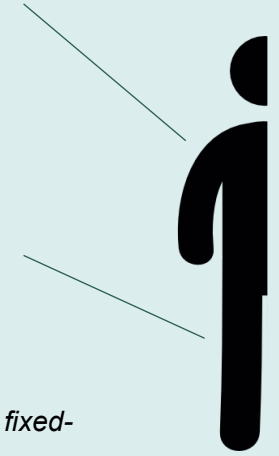
Mean changes from baseline to Week 12 in Neuro-QoL T-scores were similar for VBZ vs placebo

Neuro-QoL UEF T-score

Placebo: -3.0
Valbenazine: -1.6
Difference: 1.4; p=0.3304

Neuro-QoL LEF T-score

Placebo: 0.6
Valbenazine: -0.3
Difference: -0.9
(no statistical comparison due to fixed-sequence testing procedure)



Response was defined as a CGI-C or PGI-C score of ≤2 (“much improved” or “very much improved. CGI-C, Clinical Global Impression of Change; LEF, lower extremity function. PGI-C, Patient Global Impression of Change; UEF, upper extremity function. Furr Stimming E, et al. Lancet Neurol. 2023;22(6):494-504.

Treatment Emergent Adverse Events (TEAEs)

	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

	Placebo (n=63)	Valbenazine (n=64)
Common TEAEs,‡ n (%)		
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%)
Diarrhea	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

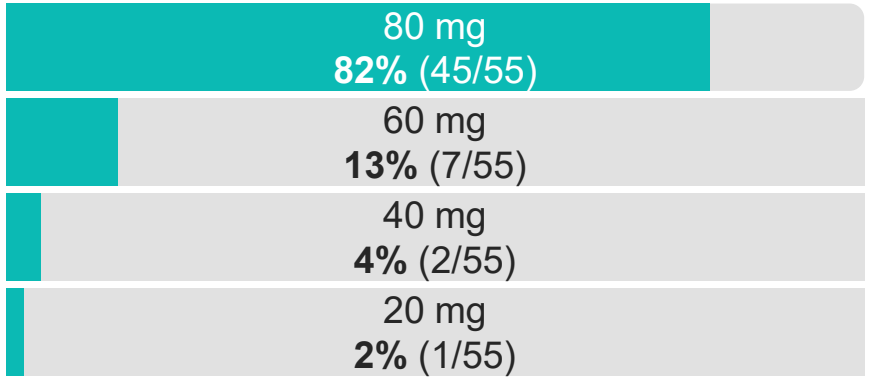
Prescribing Information

TEAE, treatment emergent adverse event.
*Serious TEAEs occurred in 2 participants in the placebo group (colon cancer and psychosis) and in 1 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% of participants in either treatment group.

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

Safety Summary

Of the 55 participants treated with VBZ who reached Week 12, most were taking 80 mg



The VBZ 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

The most common adverse reactions with VBZ (≥5% and 2x placebo) were somnolence/lethargy/sedation, urticaria, rash, insomnia

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

BARS, Barnes Akathisia Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation; TEAE, treatment emergent adverse event; UHDRS, Unified Huntington's Disease Rating Scale; VBZ, valbenazine

1. Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6):494-504. 2. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

Summary

- Treatment with VBZ once daily significantly improved chorea, as demonstrated by the mean change in UHDRS TMC scores from the screening and baseline period to the maintenance period, with the effects seen as early as Week 2
- Clinicians (CGI-C) and patients (PGI-C) reported clinically meaningful results with VBZ versus placebo
- TEAEs that affected >10% of patients treated with VBZ 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

CGI-C, Clinical Global Impression of Change; PGI-C, Patient Global Impression of Change; TEAE, treatment emergent adverse event; TMC, total maximal chorea; UHDRS, Unified Huntington's Disease Rating Scale; VBZ, valbenazine; VMAT2, vesicular monoamine transporter 2.

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

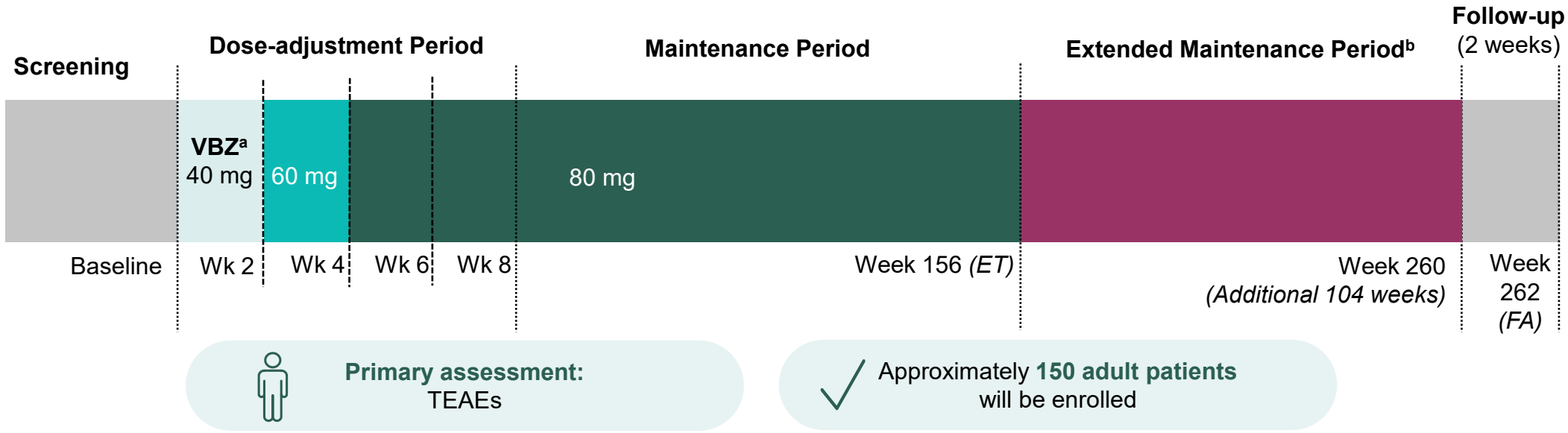
KINECT®-HD2

Ongoing, Phase 3 Open-Label, Rollover Study of Valbenazine for Chorea in HD

Study Design[1,2]

Phase 3, open-label study to evaluate the long-term safety and tolerability of valbenazine for the treatment of chorea associated with HD[1,2]

- Currently ongoing
- Amendments:
  - Concomitant use of antipsychotic therapy (at a stable dose for 30 days before baseline) was permitted at study entry
  - Optional extended maintenance for patients to continue study for an additional 104 weeks (2 years)
  - In-person and tele-visits to mimic real-world treatment



[a]Doses represent maximum daily doses during each period [b]Patients will continue the valbenazine dose level they were on when ending the previous treatment period (minimum 20mg and maximum 80 mg). Investigator may temporarily or permanently adjust dose based on response and tolerability. ET, early termination; FA, final assessment; HD, Huntington's disease; TEAE, treatment-emergent adverse event; VBZ, Valbenazine; Wk, week. 1. ClinicalTrials.gov Identifier: NCT04400331. 2. Neurocrine Biosciences. VBZ-HD-0007. Data on file.

Eligibility Criteria

Key Inclusion Criteria

- Participated in KINECT-HD* **and**
  - Study dosing completion,† **or**
  - Early termination of KINECT-HD for administrative reasons due to COVID-19‡
- **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 valbenazine) 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; HD, Huntington's disease.
*KINECT-HD is a phase 3, randomized, double-blind, placebo-controlled study completed in October 2021. †As demonstrated by completed study drug dosing through the follow-up visit. ‡Site closure related to COVID-19.
ClinicalTrials.gov Identifier NCT04102579.

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Neurocrine Medical Affairs

1-877-641-3461

Appendix

Total Functional Capacity Rating Scale (TFC)[1]* - UHDRS

- The TFC is part of the UHDRS examination and rates the person's level of independence in 5 domains
- There are several staging systems for HD but there is no singular, definitive delineation between disease stages
- One of the most commonly used staging systems is based on functional abilities using the TFC

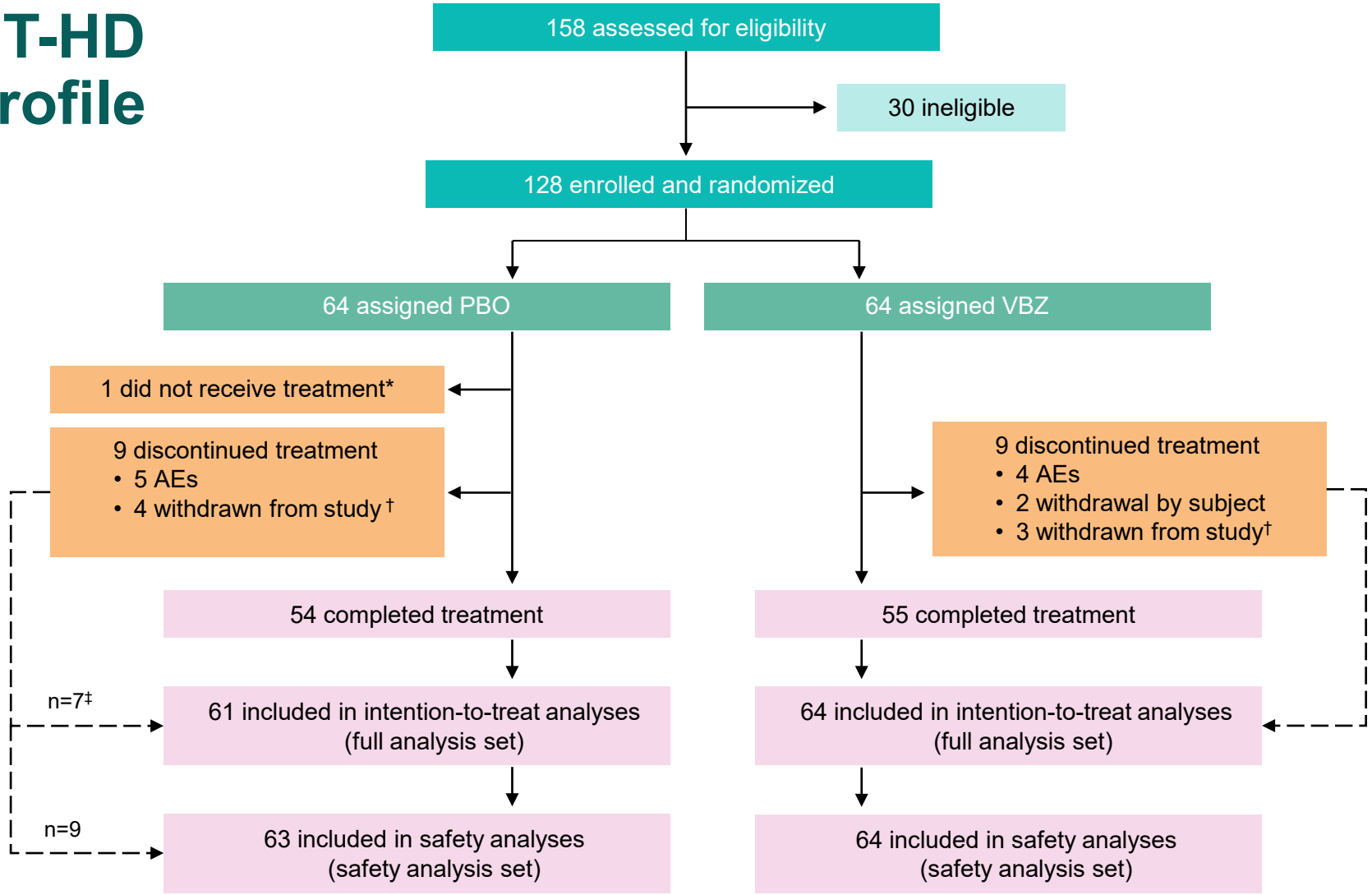
Domain	Ability	Score	Ability	Domain
Occupation	Unable	0	Total care	**Activities of daily living**
	Marginal work only	1	Gross tasks only	
	Reduced capacity for usual job	2	Minimal impairment	
	Normal	3	Normal	
Finances	Unable	0		
	Major assistance	1		
	Slight assistance	2		
	Normal	3		
Domestic Chores	Unable	0	Full-time nursing care	**Care Level**
	Impaired	1	Home for chronic care	
	Normal	2	Home	
Total (from all domains)	Range 0-13			

TFC Total Score	Stage
11-13	I
7-10	II
3-6	III
1-2	IV
0	V

*Shoulson and Fahn Staging Scale. UHDRS, Unified Huntington's Disease Ratings Scale

1. Nance M, Paulsen JS, Rosenblatt A, et al. A Physician's Guide to the Management of Huntington's Disease 3rd Edition. Huntington's Disease Society of America. 2011

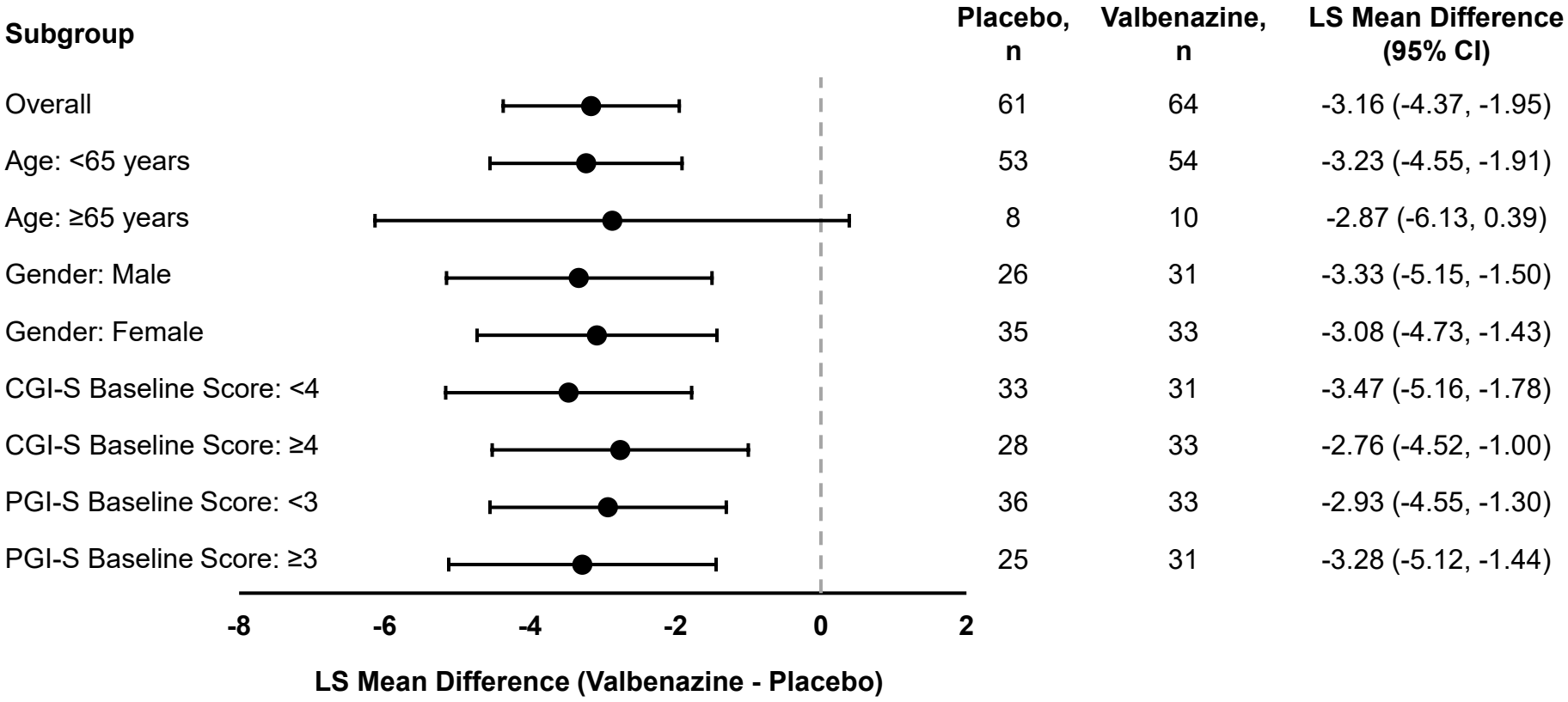
KINECT-HD Trial Profile



AE, adverse event; PBO, placebo; TMC, total maximal chorea; UHDRS, Unified Huntington's Disease Rating Scale; VBZ, valbenazine.
*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 UHDRS TMC 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.

Prespecified Subgroup Analysis

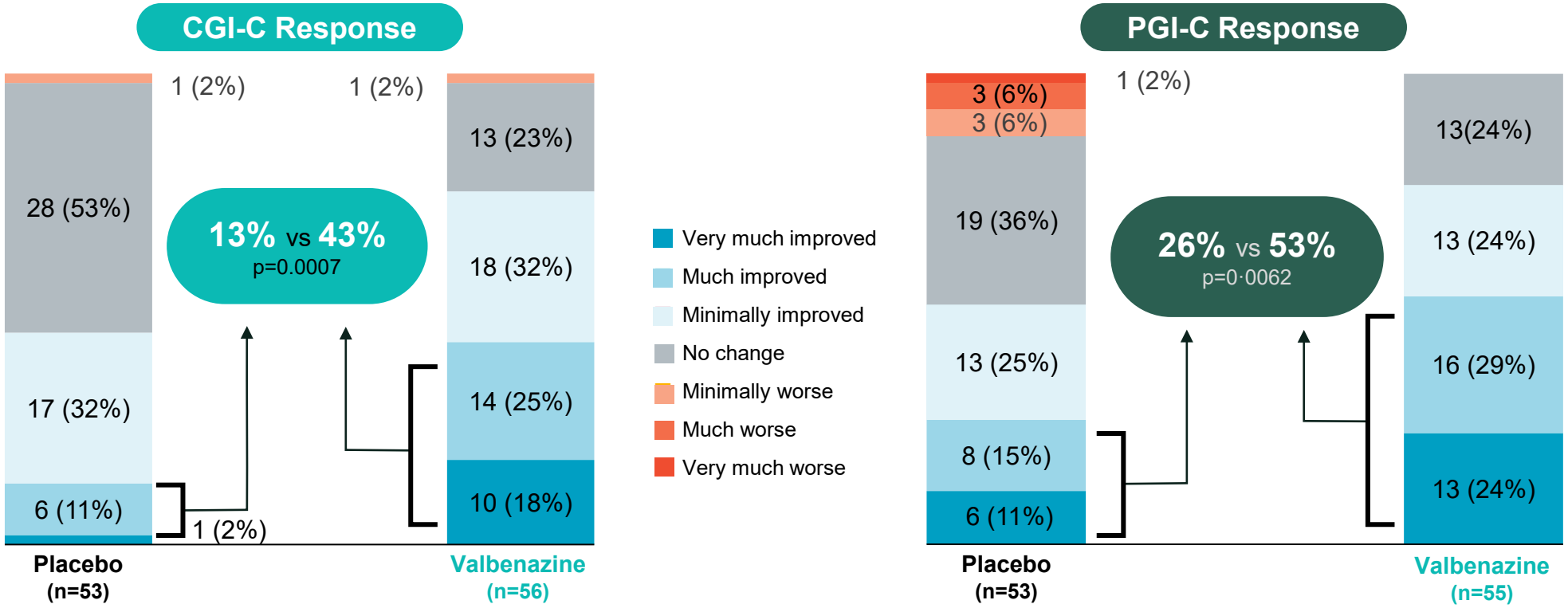
- No difference was observed in the primary efficacy endpoint when evaluated by sex or baseline CGI-S or PGI-S
- Small number of participants in the ≥65 years group prevented meaningful interpretation



CGI-S, Clinical Global Impression of Severity; CI, confidence interval; LS, least-squares; PGI-S, Patient Global Impression of Severity. Furr Stimming E, et al. *Lancet Neurol.* 2023;22(6)(supp):1-16.

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

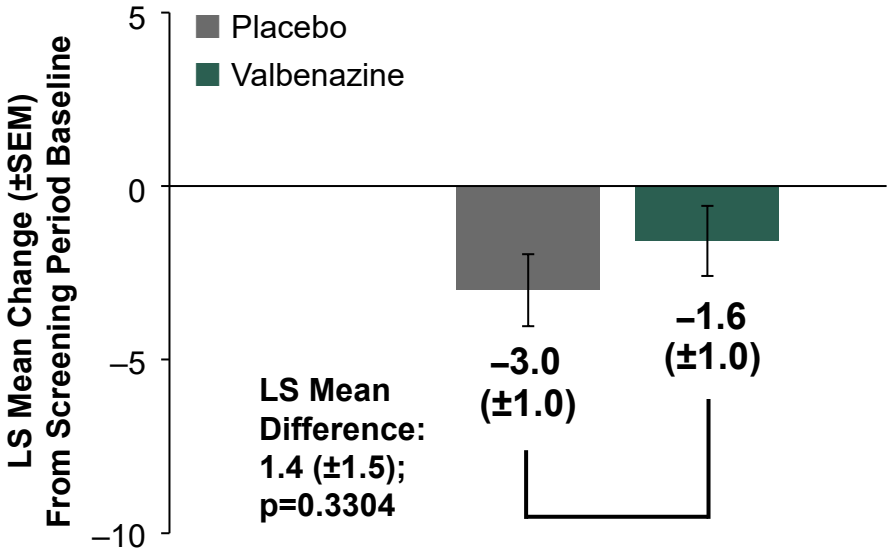


CGI-C, Clinical Global Impression of Change; PGI-C, Patient Global Impression of Change.
Graphs represent the distribution of CGI-C and PGI-C scores by treatment group, with purple brackets indicating the percentage and number of participants who met the threshold for good clinical response, defined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

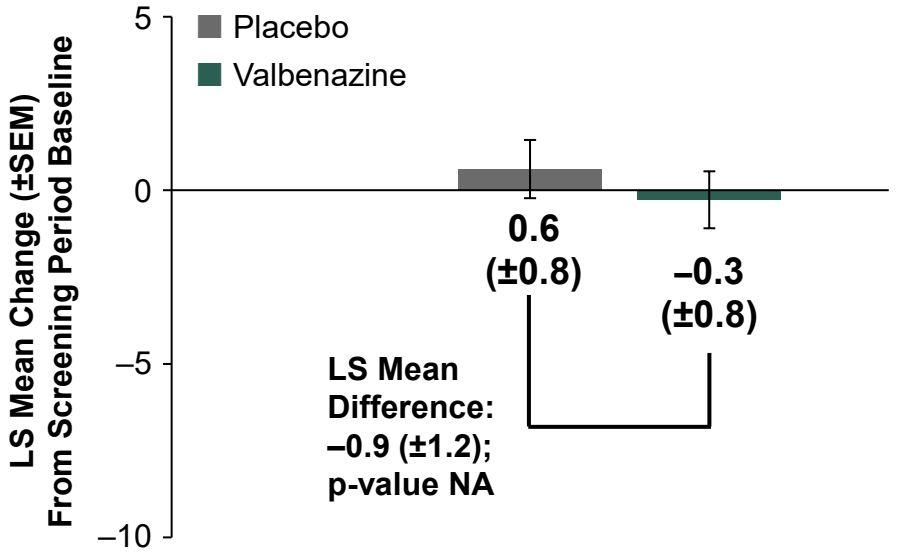
Secondary Endpoints: Neuro-QoL

- 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

Neuro-QoL UEF T-score



Neuro-QoL LEF T-score



LEF, lower extremity function; LS, least squares; NA, not applicable; Neuro QoL, Quality of Life in Neurological Disorders; SEM, standard error mean; UEF, upper extremity function.

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

HD is Caused by a Mutation in the Huntingtin Gene (HTT)

CAG repeats within HTT are associated with penetrance of HD and timing of onset, with larger CAG repeats associated with younger disease onset[1]

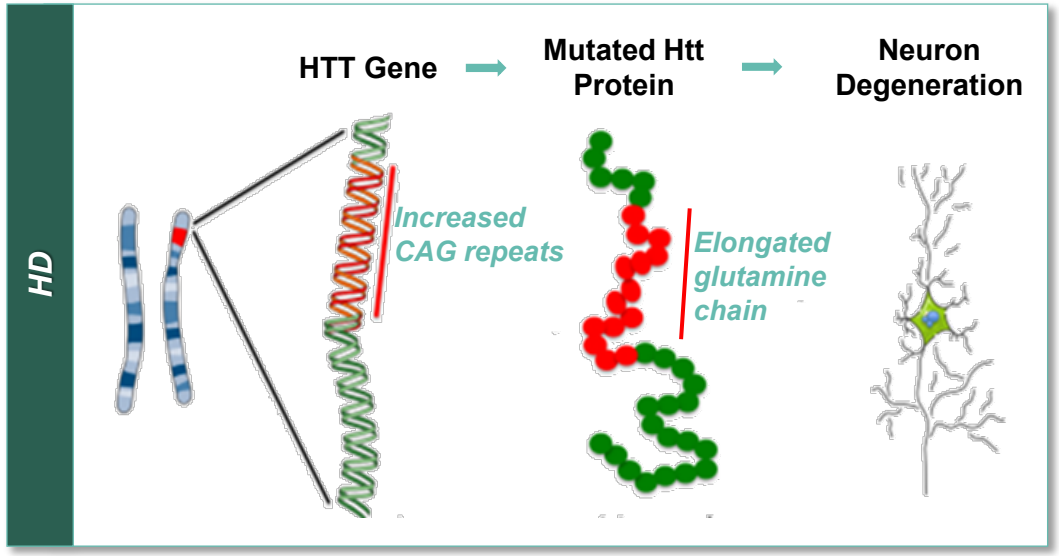


Image courtesy of Euro Stem Cell[2]

Significance of CAG repeats in the huntingtin gene[1]

CAG Repeat Length	Interpretation	
< 27	Normal	Normal
27 - 35	Intermediate	**Not at risk of developing HD symptoms** but due to instability of CAG repeats, potential risk of having a child with expanded CAG repeats
36 - 39	Reduced penetrance	**May or may not develop symptoms of HD**. Unstable CAG repeats → future generations at risk
≥ 40	Affected	Development of HD symptoms

CAG, cytosine, adenine, and guanine; HD, Huntington's disease. HTT; huntingtin gene; Htt, huntingtin protein.

1. Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition*. Huntington's Disease Society of America. 2011. 2. EuroStemCell. Accessed July 7, 2021. https://www.eurostemcell.org/huntingtons-disease-how-could-stem-cells-help.

Face: Moderate

Eyebrow elevation, intermittent excessive blinking, "winking," intermittent frontalis muscle contraction

Oral-Buccal-Lingual: Severe

Constant opening and closing of jaw with associated lip pursing, lip smacking, frequent tongue protrusion

Trunk: Mild

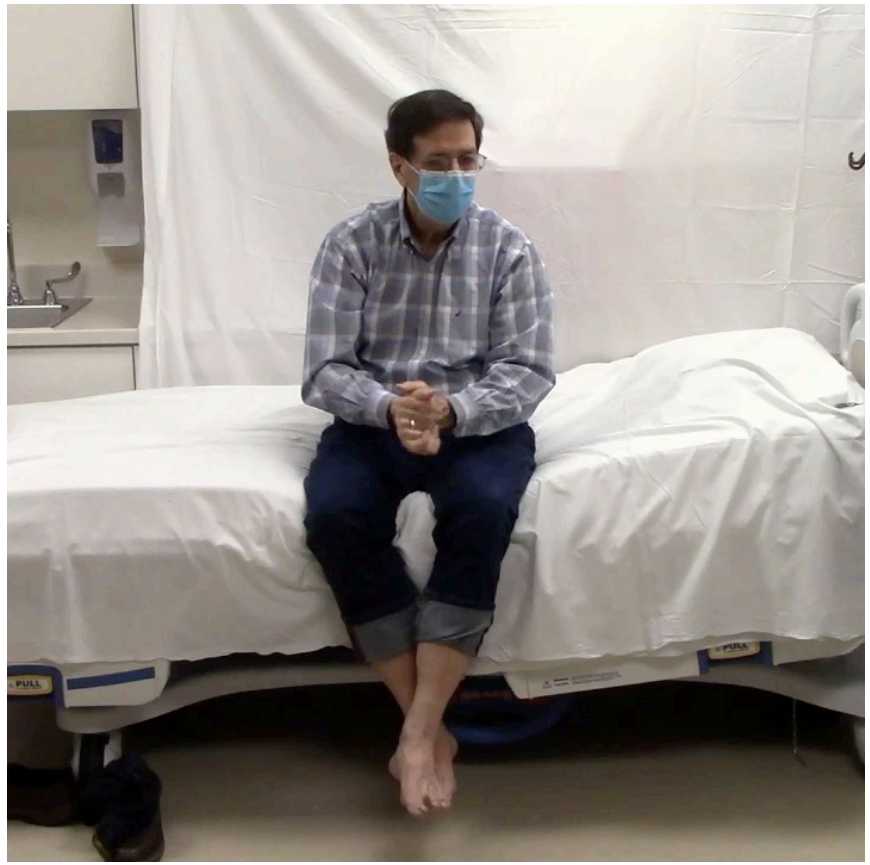
Slow, irregular truncal sway

THESE PATIENTS HAVE CONSENTED TO NEUROCRINE'S USE OF THEIR VIDEOS AND PROTECTED HEALTH INFORMATION.

Upper Extremities: Severe

Constant, irregular fingers, arms and shoulder high amplitude movements, attempt to mask chorea as voluntary movements

Lower Extremities: Moderate



Constant distal flexion/extension and inversion of foot, fanning of toes, infrequent sudden proximal movements

THESE PATIENTS HAVE CONSENTED TO NEUROCRINE'S USE OF THEIR VIDEOS AND PROTECTED HEALTH INFORMATION.

Gait: Mild and Severe

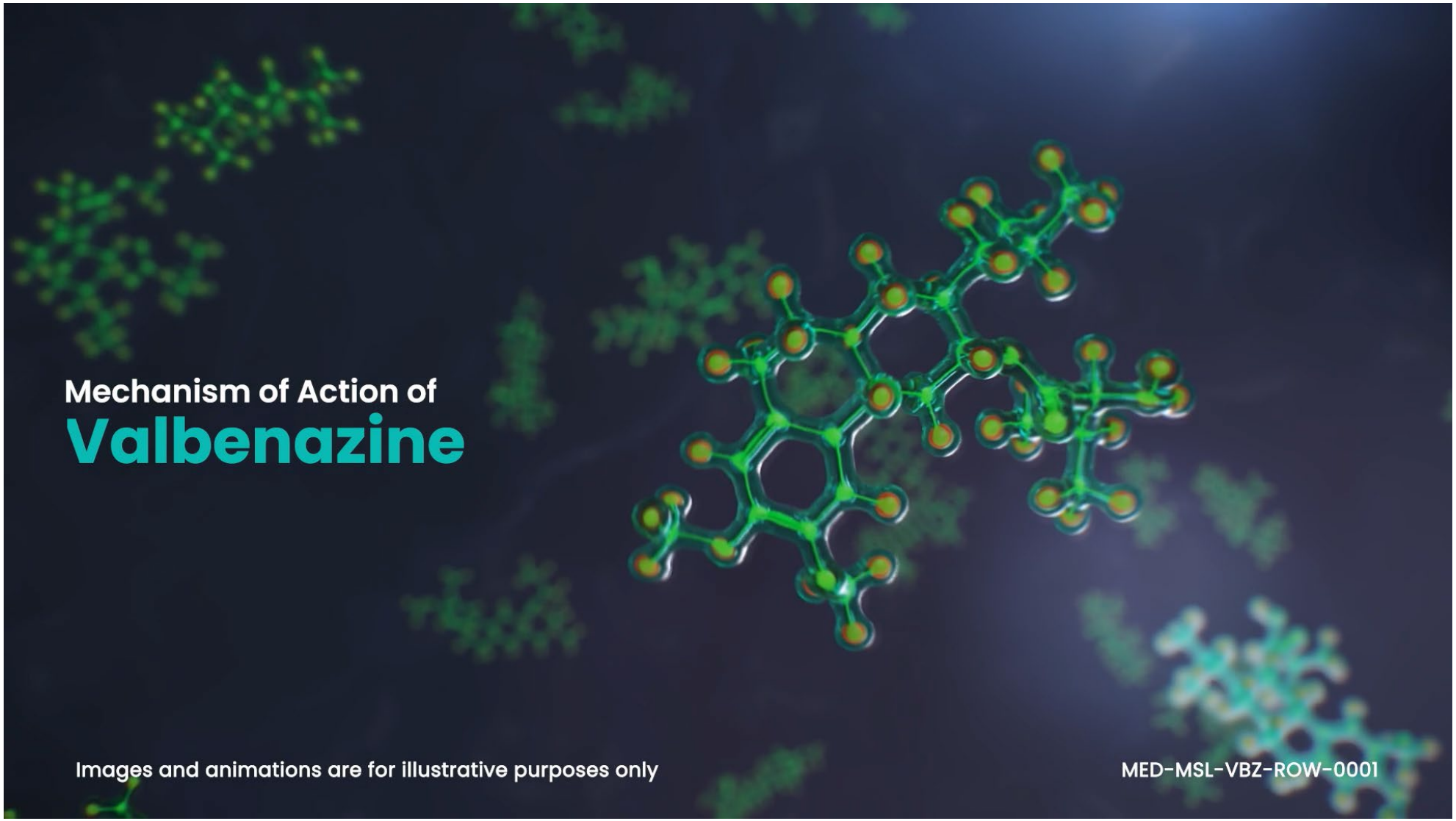
Foot inversion, slightly irregular steps, wider-based and unsteady on turn

Wide-based bouncing gait, irregular steps, truncal sway, knees buckling, with upper extremity and truncal chorea contributing to unsteadiness

THESE PATIENTS HAVE CONSENTED TO NEUROCRINE'S USE OF THEIR VIDEOS AND PROTECTED HEALTH INFORMATION.

HD Chorea Mechanism of Disease

Valbenazine Mechanism of Action



Valbenazine Overview

Valbenazine[1]

Typical dosage range	40-80 mg, 1 capsule once daily
Dosage forms	Capsules: 40, 60, 80 mg
Active metabolites	[+]-α-HTBZ, selective for VMAT2 only, with no appreciable binding affinity for dopaminergic, serotonergic, adrenergic, or histaminergic receptors[2]
Elimination half-life	15–22 hours

HTBZ, dihydrotetrabenazine; MDD, major depressive disorder; VBZ, valbenazine; VMAT2, vesicular monoamine transporter type 2.

1. Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia*. 3rd ed. Washington, DC: American Psychiatric Association; 2020. https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841. Accessed April 20, 2021. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA

Valbenazine Overview (cont'd)

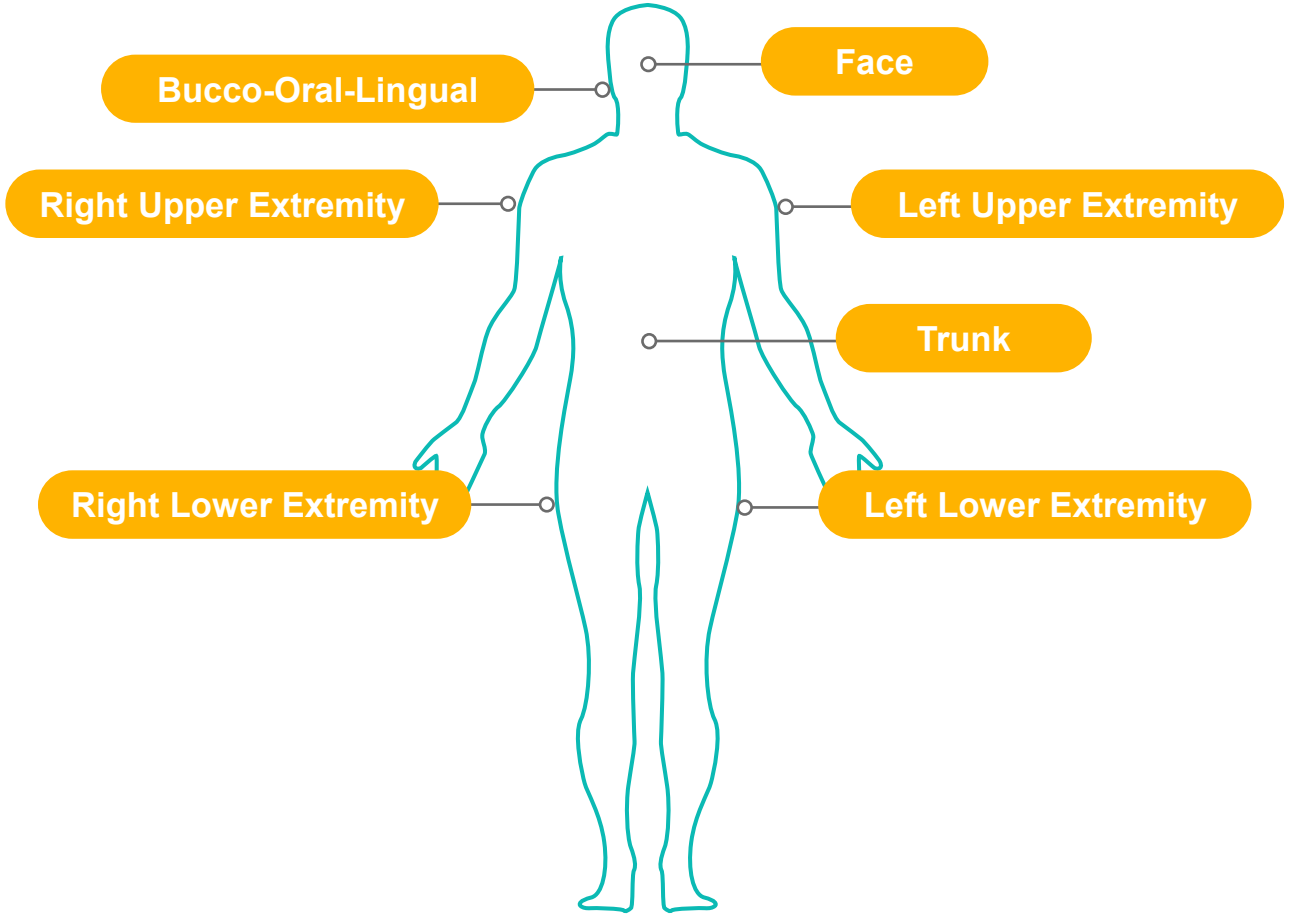
Valbenazine[1]

Hepatic impairment	Maximum dose of 40 mg daily for moderate to severe impairment
Renal impairment	Dosage adjustment not necessary
Effect of food on bioavailability	Taken with or without food
Geriatric use	No dose adjustment required[2]

VBZ, valbenazine.

1. Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia*. 3rd ed. Washington, DC: American Psychiatric Association; 2020. https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841. Accessed April 20, 2021. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA

Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) Score Rates Chorea in 7 Body Regions[1]



UHDRS Motor Assessment Chorea Scale	
Severity	
0	Absent
1	Slight/intermittent
2	Mild/common or moderate/intermittent
3	Moderate/common
4	Marked/prolonged

TMC score is the sum of the severity scores for each body region and ranges from **0 to 28**

The UHDRS TMC score is often used to assess the appropriateness and effectiveness of treatment interventions

TMC, total maximal chorea; UHRDS, Unified Huntington's Disease Rating Scale.

1. Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition.* Huntington's Disease Society of America. 2011.

The Quality of Life in Neurological Disorders (Neuro-QoL) Functional Scales

- The Neuro-QoL, a patient-reported outcome (PRO), is a collection of psychometrically sound, clinically relevant, health-related quality of life and physical function measurement tools for individuals with neurological conditions[1]
- The Neuro-QoL has been demonstrated to be a valid tool for assessing patient-reported physical functioning measures in participants with HD[2]

Upper Extremity Function Short Form

Lower Extremity Function Short Form

8 questions each

Assess physical functioning of daily life tasks requiring motor coordination

Rated 1 (unable to do) to 5 (without any difficulty)

Maximum raw score on each is 40

Total raw scores are converted to T-scores

UEF Raw Score	T Score
8	12.8
40	53.8
LEF Raw Score	**T Score**
8	16.5
40	58.6

LEF, lower extremity function; UEF, upper extremity function.

1. National Institute of Neurological Disorders and Stroke (NINDS). User Manual for the Quality of Life in Neurological Disorders (Neuro-QoL) Measures, Version 2.0, March 2015. 2. Carlozzi NE et al. J of Huntington's Disease. 8,4:467-482;2019.

Valbenazine Package Insert Adverse Reactions:

Adverse Reactions in the 12-Week KINECT-HD Study Reported at ≥4% and >Placebo[1,2]

	Placebo (n=63)	Valbenazine (n=64)
Adverse Reaction		
Somnolence, lethargy, sedation	2 (3.2%)*	12 (18.8%)†
Fatigue	6 (9.5%)	9 (14.1%)
Urticaria	0	6 (9.4%)
Rash	0	5 (7.8%)
Akathisia	3 (4.8%)	4 (6.3%)
Insomnia, middle insomnia	1 (1.6%)	4 (6.3%)
Back pain	0	3 (4.7%)
Depression, depressed mood	1 (1.6%)‡	3 (4.7%)§
Diarrhea	1 (1.6%)	3 (4.7%)
Nausea	0	3 (4.7%)

*Reactions of somnolence
† Reactions of somnolence n=10 (15.6%), lethargy n=1 (1.6%), sedation n=1 (1.6%)
‡Reaction of depression
≠Reactions of depression n=2 (3.1%), depressed mood n=1 (1.6%)

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc. 2. Neurocrine Biosciences. VBZ-HD-0003. Data on file.