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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WARNING: DEPRESSION AND SUICIDAL IDEATION AND BEHAVIOR IN PATIENTS WITH HUNTINGTON'S DISEASE[1]

VMAT2 inhibitors, including INGREZZA, can increase the risk of depression and suicidal thoughts and behavior in patients with Huntington's disease. Anyone considering the use of INGREZZA must balance the risks of depression and suicidal ideation and behavior 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. Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.

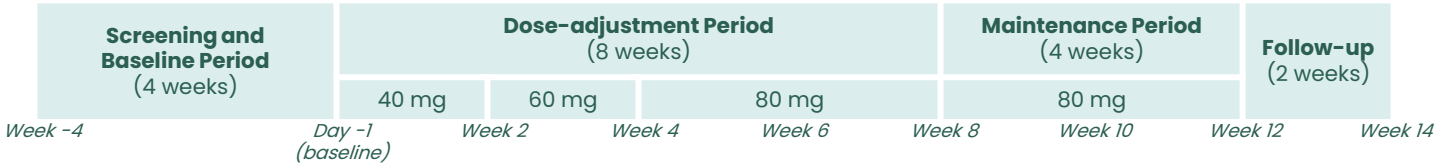
Please see the full INGREZZA FDA-approved Prescribing Information, including Boxed Warning, for additional Important Safety Information

Study Design

128 adults with motor manifest Huntington's disease (HD) were randomized (1:1) to **12 weeks of double-blind treatment with valbenazine or placebo**

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

Efficacy, safety, and tolerability of valbenazine were assessed throughout the 12-week treatment period and the end of 2-week no-drug follow-up period



Dose levels represent maximum daily dosages of valbenazine for each 2-week interval in the dose-adjustment period and for the 4-week maintenance period. Based on tolerability as judged by the investigator, reductions to the next lower dose were allowed (e.g., 80 mg → 60 mg).

Key Inclusion Criteria

- Adults 18–75 years with a diagnosis of manifest HD
- Expanded CAG repeat (≥37) in *HTT* gene
- Unified Huntington's Disease Rating Scale® (UHDRS®) Total Maximal Chorea (TMC) Score ≥8 and Total Functional Capacity Score ≥5

Key Exclusion Criteria

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

ClinicalTrials.gov identifier: NCT04102579

Study Population

Full-analysis set (N=125)

61	placebo
64	valbenazine

Safety-analysis set (N=127)

63	placebo
64	valbenazine

In the full-analysis set:

- 109 (85%) of participants **completed study treatment**
  - 54 receiving placebo
  - 55 receiving valbenazine
- Baseline demographics and disease characteristics were **similar between treatment groups**

Demographics

Female	**54%** (68/125)
White	**96%** (120/125)
Not Hispanic or Latino	**94%** (117/125)
Mean age	**53.7** ±10.8

Baseline Characteristics

Mean CAG repeat length	**43.4** ±3.2
Mean TMC score	**12.2** ±2.6
CGI-S ≥4[a]	**49%** (61/125)
PGI-S ≥3[a]	**45%** (56/125)

[a]Represents moderate or worse severity

CGI-S, Clinical Global Impression of Severity; FDA, US Food and Drug Administration; HD, Huntington's disease; PGI-S, Patient Global Impression of Severity; TMC, Total Maximal Chorea; UHDRS®, Unified Huntington's Disease Rating Scale; VMAT2, vesicular monoamine transporter 2.

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

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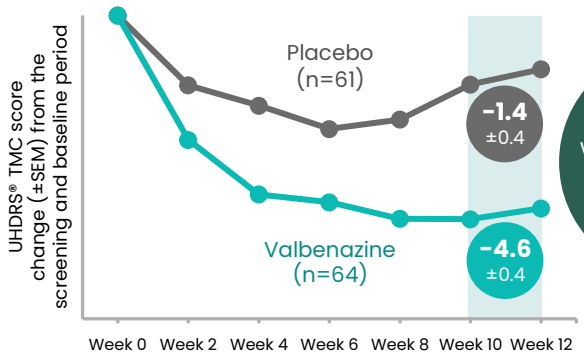
Efficacy of valbenazine for treatment of chorea

Primary outcome:

Mean change in **UHDRS® TMC score** from the screening and baseline period to the maintenance period as assessed by on-site study investigators

- **Screening and baseline period:** average of screening and baseline values of each participant
- **Maintenance period:** average of week 10 and week 12 values of each participant

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



UHDRS® TMC mean change with valbenazine: **-3.2 (±0.6)**
95%CI: -4.4, -2.0
p<0.0001

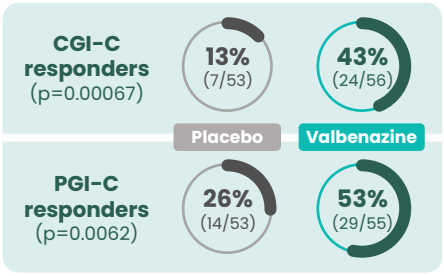
Secondary outcomes:

Score of **very much improved** or **much improved** at week 12 on:

- Clinical Global Impression of Change (CGI-C)
- Patient Global Impression of Change (PGI-C)

Mean change from baseline to week 12 in **Quality of Life in Neurological Disorders (Neuro-QoL)** T-scores:

- Upper Extremity Function (UEF)
- Lower Extremity Function (LEF)



Neuro-QoL UEF T-score

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

Neuro-QoL LEF T-score

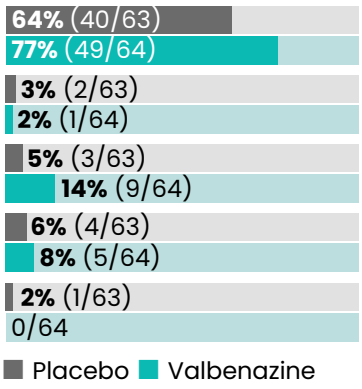
Placebo: 0.6
Valbenazine: -0.3
Difference: -0.9
(no statistical comparison due to fixed-sequence testing procedure)

Statistically significant **improvements in CGI-C and PGI-C response status** were found with valbenazine versus placebo

Safety and tolerability of valbenazine

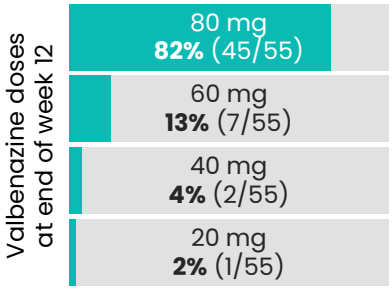
Treatment-emergent adverse events (TEAEs)

- The most commonly reported TEAEs with higher incidence in the valbenazine group were **somnolence** and **fatigue**



Tolerability of valbenazine

- In participants taking valbenazine at the week 12 visit, **most were taking the highest dose (80 mg)**



In summary...

KINECT®-HD results support the efficacy of valbenazine in individuals with chorea associated with Huntington's disease

For questions, please contact Neurocrine Medical Information at: medinfo@neurocrine.com

[a]Death caused by colon cancer, judged by the investigator as being unlikely to be related to the study drug. CGI-C, Clinical Global Impression of Change; CI, confidence interval; LEF, Lower Extremity Function; Neuro-QoL, Quality of Life in Neurological Disorders; PGI-C, Patient Global Impression of Change; SEM, standard error of the mean; TEAE, treatment-emergent adverse event; TMC, Total Maximal Chorea; UEF, Upper Extremity Function; UHDRS®, Unified Huntington's Disease Rating Scale; VMAT2, vesicular monoamine transporter 2.

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