(p) 877-641-3461
(f) 913-451-6409

12780 El Camino Real San Diego, CA 92130
http://www.neurocrinemedical.com/

INGREZZA® (valbenazine) Capsules Clinical Development in Patients with Chorea Associated with Huntington's Disease

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the use of INGREZZA capsules for the treatment of chorea associated with Huntington's disease.

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with chorea associated with Huntington's disease.[1]

The clinical development program for valbenazine (VBZ) in Huntington's disease (HD) chorea includes **KINECT®-HD,** a 12-week phase 3, randomized, double-blind, placebo-controlled study, and **KINECT®-HD2** an ongoing phase 3, open-label, rollover study. This summary is to respond to your request for a summary of these clinical studies.

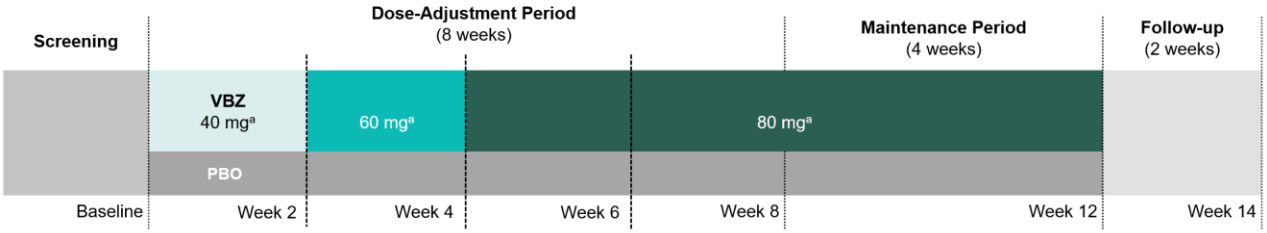
Please refer to the separately attached INGREZZA FDA-approved full Prescribing Information and the Important Safety Information, including a Boxed Warning, for more information.

KINECT®-HD

Study Design[2,3]

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. The study enrolled 128 participants (18-75 years old) with a genetically confirmed diagnosis of HD with an expanded CAG repeat (≥37) in the Huntingtin gene.

Participants were randomized 1:1 to either valbenazine or placebo for 12 weeks, which included an 8-week dose-adjustment period (40 mg, 60 mg, and 80 mg, as tolerated) followed by a 4-week stable-dose maintenance period.



[a]Doses represent maximum daily doses during each 2-week interval in the dose-adjustment period and during the maintenance period. PBO, placebo; VBZ, valbenazine.

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(f) 913-451-6409
12780 El Camino Real San Diego, CA 92130
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Results[3]

Key Baseline Characteristics

Baseline characteristics were generally similar between placebo and valbenazine groups (**Table 1**).

Table 1. Baseline Characteristics[a,3]

	Placebo (n=61)	Valbenazine (n=64)
Age, mean (SD), years	53.3 (11.4)	54.1 (10.1)
Sex		
Female, n (%)	35 (57.4)	33 (51.6)
Male, n (%)	26 (42.6)	31 (48.4)
Race n (%)		
White,	60 (98.4)	60 (93.8)
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, mean (SD) kg/m^2	27.4 (5.7)	26.6 (5.6)
CAG repeat length, mean (SD)	43.4 (3.0)	43.5 (3.3)
UHDRS® TMC score, mean (SD)[b]	12.1 (2.8)	12.2 (2.3)
CGI-S score ≥4, n (%)[c]	28 (45.9)	33 (51.6)
PGI-S score ≥3, n (%)[d]	25 (41.0)	31 (48.4)
SDQ total score	5.2 (6.2)	4.9 (6.2)
MoCA score	24.2 (3.2)	22.9 (4.3)

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.
[a]Participants with ≥1 evaluable post-baseline UHDRS® TMC assessment
[b]For screening period baseline (average of screening and Day -1 assessments)
[c] Investigator rating of "moderately ill" to "among the most extremely ill" for chorea.
[d] Participant self-rating of "moderate" to "very severe" for chorea.

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Efficacy[3]

Outcomes

The primary efficacy endpoint in KINECT-HD was the change from baseline (average of screening and baseline score) to maintenance (average of week 10 and week 12) in the Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) score.

Secondary efficacy endpoints included Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) response at week 12 as well as the mean change from baseline to week 12 in the Quality of Life in Neurological Disorders (Neuro-QoL) Upper and Lower Extremity Function scores.

Additionally, the changes from the screening and baseline period to each postbaseline study visit (weeks 2 through 12) in the TMC was assessed as a prespecified exploratory endpoint.

Results

The study met the primary endpoint of reduction in severity of chorea, as measured by change in the UHDRS TMC score from baseline to the average score at weeks 10 and 12 (**Figure 1**). Least-squares mean changes from the screening and baseline period to maintenance period in the UHDRS TMC score were **–4.6 for valbenazine** and **–1.4 for placebo** with a statistically significant mean difference of –3.2; p<0.0001).

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 (**Figure 2**).

Figure 1: Mean Change from Screening and Baseline to Maintenance in UHDRS TMC

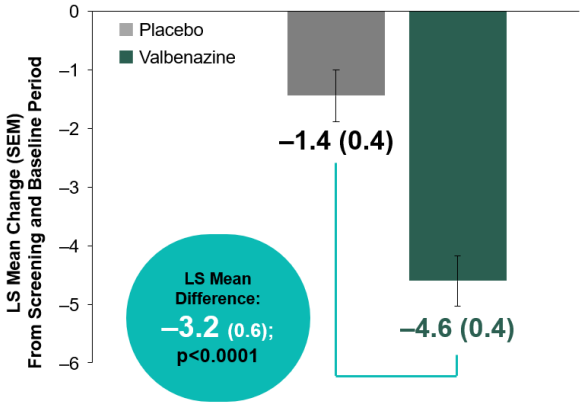
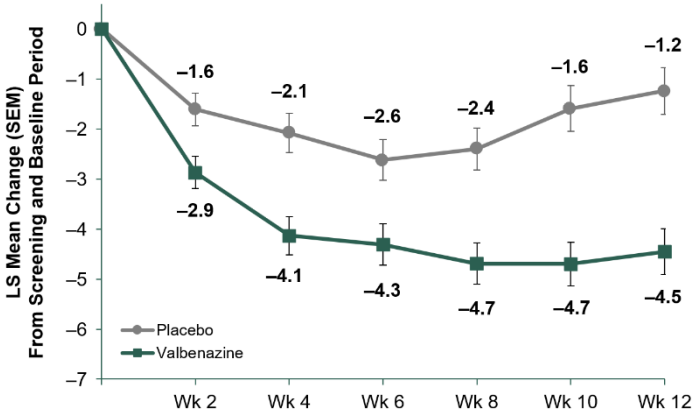


Figure 2: Exploratory Endpoint: Mean Change from Screening and Baseline Period by Study Visit



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.

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 (**Figure 3**).

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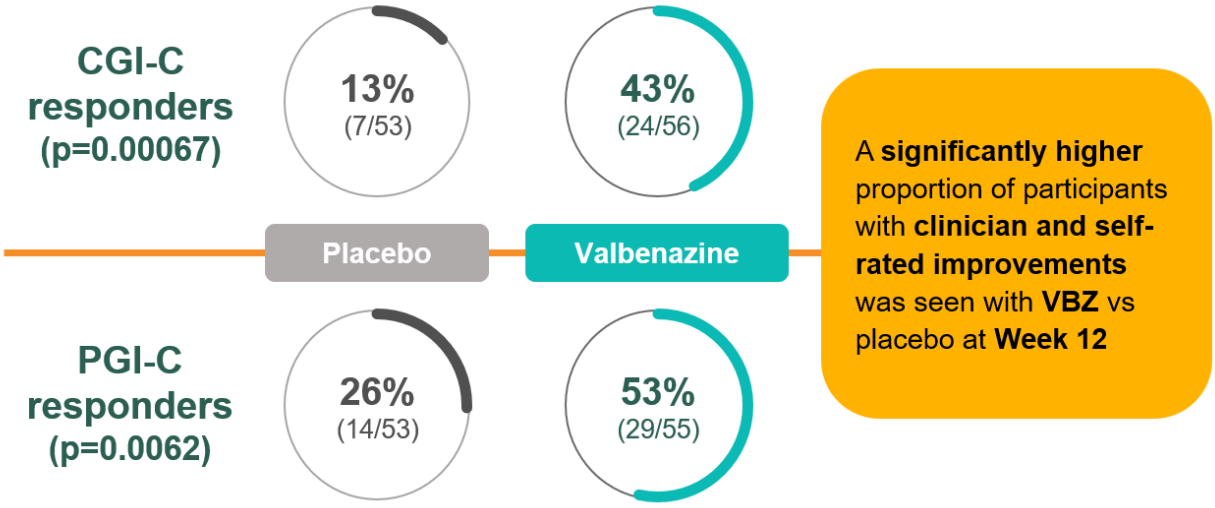
Figure 3: CGI-C and PGI-C Response* Rates at Week 12[3]



*Participants with CGI-C or PGI-C scores of either a 1 ("very much improved") or a 2 ("much improved") were classified as responders. TMC, Total Maximal Chorea; UHDRS, Unified Huntington's Disease Rating Scale.

However, the change from baseline to week 12 was not statistically significant in the Neuro-QoL T-scores. Results were similar for valbenazine versus placebo; Upper Extremity Function (-1.58 vs -3.00, not significant) and Lower Extremity Function (-0.27 vs 0.61, p value not conducted per fixed-sequence testing procedure).

Safety[3]

In the 12-week KINECT-HD study, the most common treatment-emergent adverse events (TEAEs) with valbenazine were somnolence, fatigue and falls. TEAEs reported in ≥5% of participants for either valbenazine or placebo groups are listed in **Table 2**.

Please refer to the attachments for Important Safety Information, including a Boxed Warning.

Table 2: TEAEs from KINECT-HD[3]

Treatment-Emergent Adverse Events (TEAEs)	Placebo (n=63)	Valbenazine (n=64)
Summary, n (%)		
Overall TEAEs	40 (63.5)	49 (76.6)
Serious TEAEs	2 (3.2)	1 (1.6)
TEAEs resulting in discontinuation	4 (6.3)	5 (7.8)
TEAEs resulting in death[a]	1 (1.6)	0
Common TEAEs,[b] n (%)		

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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

[a] Due to colon cancer; judged by investigator as unlikely related to study treatment.
[b] As reported in ≥5% of participants in either treatment group.

Nine (14%) participants in the valbenazine group had a dose reduction due to TEAE, 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 due to TEAEs was similar between treatment groups (**Table 2**). Three participants had urticaria and 2 participants had rash resulting in discontinuation of valbenazine. All cases resolved after discontinuation.

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 with known allergy to shellfish who reported consuming shellfish a day before experiencing angioedema. The investigator judged this event as unlikely to be related to study treatment. The participant continued treatment and completed the study on 80 mg.

No clinically important differences in vital signs, laboratory results, and ECG parameters were observed between treatment groups.

Additionally, mean changes from baseline to week 12 in additional safety scales were similar between treatment groups: Hospital Anxiety and Depression Scale (HADS), Barnes Akathisia Rating Scale (BARS), and items from the Unified Huntington's Disease Rating Scale (UHDRS) motor assessment for parkinsonism.

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(f) 913-451-6409
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KINECT-HD2

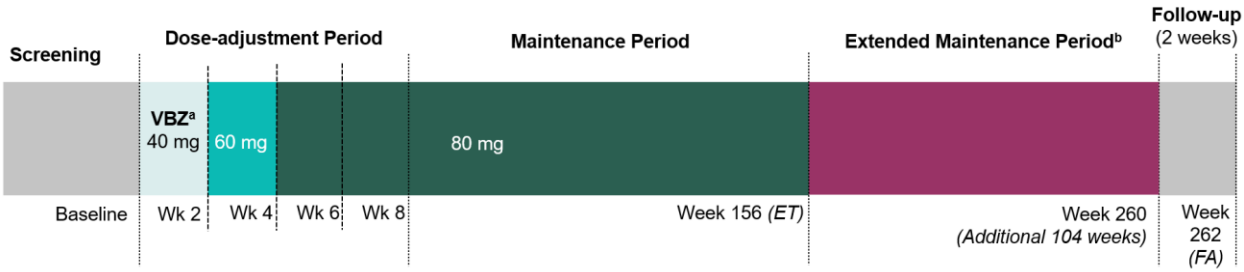
Study Design[4,5]

KINECT-HD2 is an ongoing, Phase 3, open-label, rollover study to evaluate the long-term safety and tolerability of valbenazine for the treatment of chorea associated with HD.

Participant enrollment will include up to 150 individuals who completed KINECT-HD (or had an early termination from KINECT-HD for administration reasons due to COVID-19) and patients who did not participate in KINECT-HD (de novo), but meet the inclusion criteria of KINECT-HD.

The KINECT-HD2 inclusion criteria were later amended to allow inclusion of participants on stable background antipsychotic therapy (consistent dose for 30 days before baseline) and an optional extended maintenance period.

All participants start valbenazine treatment at 40 mg, with increases to 60 and 80 mg (at weeks 2 and 4, respectively) with a target maintenance dose of 80 mg. During the dose-adjustment period, doses may be reduced multiple times. During the maintenance period, the dose may be reduced once if not tolerated, or increased by one dose level if chorea worsens.



[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.

The study is currently ongoing.
Results of the interim analysis are described below.

For more information on the KINECT-HD2 Study, please visit
https://huntingtonstudygroup.org/current-clinical-trials/kinect-hd2/

Interim Analysis: Study Participants[5]

A preplanned interim analysis was conducted in all participants who received at least 1 dose of study drug. At the time of the interim analysis, 127 participants were enrolled: 98 continuing from KINECT-HD and 29 entering de novo.

Demographics and baseline characteristics of the 125 participants who received at least 1 dose of study drug are presented in Table 3.

- 102 (81.6%) of these participants received at least 1 dose of valbenazine 80 mg
- 79 (63.2%) had been taking valbenazine 80 mg for ≥3 months

Table 3: Demographics and Baseline Characteristics[5]

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	Participants (N=125)
Demographics	
Age, mean (SD), years	54.8 (11.5)
Female, n (%)	65 (52.0)
White, n (%)[a]	118 (94.4)
Not Hispanic or Latino, n (%)	121 (96.8)
Body mass index, mean (SD), kg/m2	26.7 (5.7)
Baseline characteristics	
CAG repeat length, mean (SD)	43.5 (3.4)
UHDRS® TMC score, mean (SD)[b]	11.9 (3.5)
CGI-S score ≥4, n (%)[c]	65 (52.0)
PGI-S score ≥3, n (%)[c]	67 (53.6)

[a]Additional self-reported races were as follows: Black/African American (n=4) and other/multiple (n=3).

[b]Score range: 0 to 28, with higher scores indicating more severe chorea.

[c]Represents moderate or worse severity of chorea symptoms per clinician assessment or patient self-report. CGI-S, Clinical Global Impression of Severity; PGI-S, Patient Global Impression of Severity; SD, standard deviation; TMC, Total Maximal Chorea; UHDRS, Unified Huntington's Disease Rating Scale.

Interim Results: Efficacy[5]

Outcomes

The preplanned interim analysis evaluated the maintenance effect of valbenazine on chorea associated with HD evaluating mean changes from baseline in TMC score, response status for CGI-C and PGI-C defined as a score ≤2 ("very much improved" or "much improved"), and TEAEs.

Results

In the interim analysis, the mean reduction in TMC score was observed by week 2 with valbenazine starting dose (40 mg), and a sustained improvement was observed from week 8 to week 50 with the maintenance dose (up to 80 mg) (**Figure 4**).

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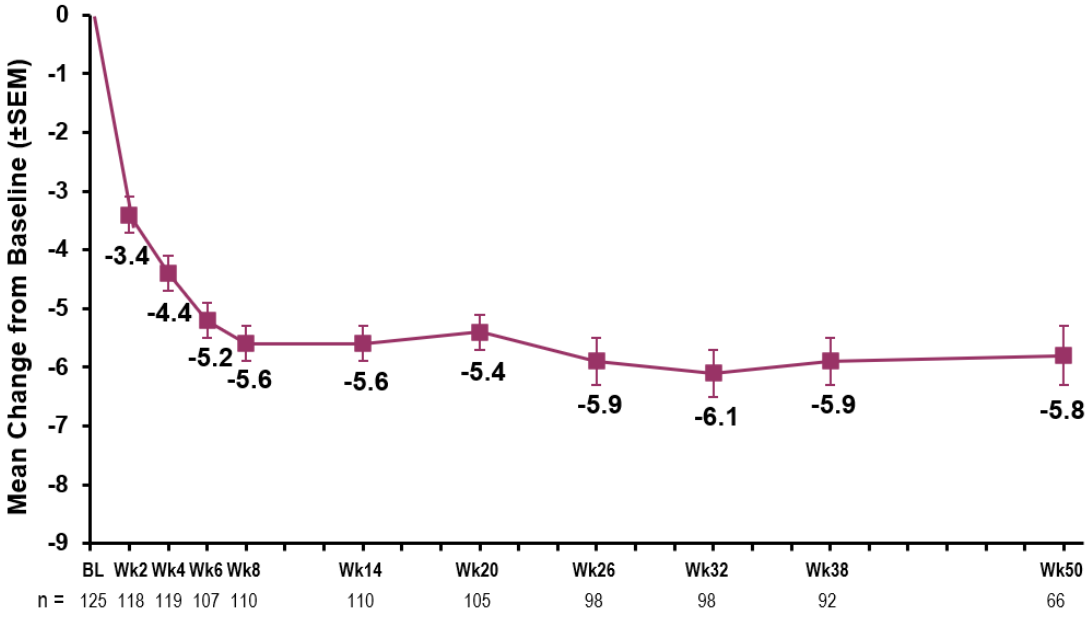
Figure 4: Mean Changes in UHDRS TMC Score by Study Visit[5]

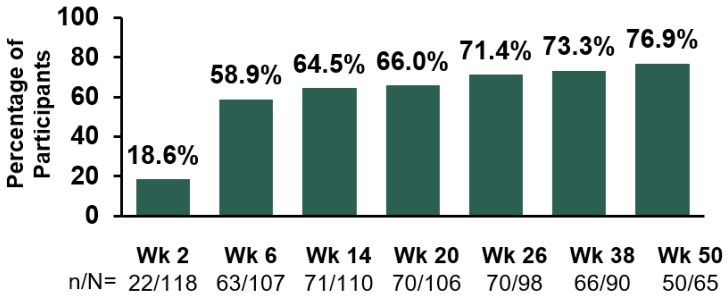


BL, baseline; n, number of participants; SEM, standard error of the mean; TMC, total maximal chorea; UHDRS, Unified Huntington's Disease Rating Scale; Wk, week.

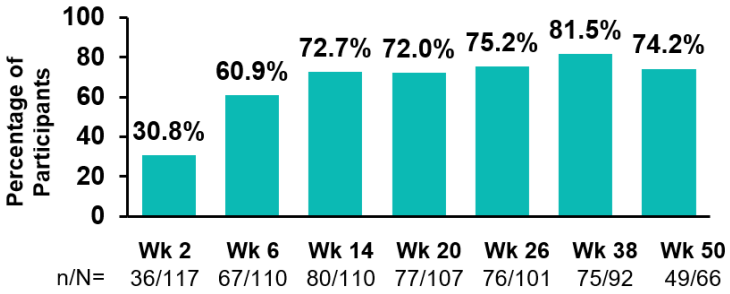
Approximately 75% of participants had chorea that was considered "much improved" or "very much improved" at Week 50, based on investigator assessments (CGI-C) and participant self-reports (PGI-C) (**Figure 5, A and B**).

Figure 5: CGI-C and PGI-C Response Status by Visit

A. CGI-C Score ≤2



B. PGI-C Score ≤2



BL, baseline; CGI-C, Clinical Global Impression of Change; n/N,number of participants meeting response threshold / number of participants with an available assessment; PGI-C, Patient Global Impression of Change; UHDRS, Unified Huntington's Disease Rating Scale; Wk, week.

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(f) 913-451-6409
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Interim Results: Safety[5]

At the time the interim analysis was conducted, 125 participants received treatment, of which 119 (95.2%) reported at least 1 TEAE (Table 4).

The most commonly reported in the interim analysis TEAEs were fall (30.4%), somnolence (24.0%), and fatigue (24.0%). No deaths were reported up to the time of analysis.

Table 4: TEAEs from KINECT-HD2[5]

Treatment-Emergent Adverse Events (TEAEs)	Participants (N=125)
Summary, n (%)	
Overall TEAEs	119 (95.2)
Serious TEAEs[a]	17 (13.6)
TEAEs leading to discontinuation of study drug[b]	17 (13.6)
Common TEAEs, n (%)[c]	
Fall	38 (30.4)
Somnolence	30 (24.0)
Fatigue	30 (24.0)
COVID-19	19 (15.2)
Anxiety	18 (14.4)
Depression	14 (11.2)
Insomnia	13 (10.4)

[a]Serious TEAEs in ≥2 participants were suicide attempt (n=3) and depression (n=2).

[b]TEAEs leading to discontinuation of study drug in ≥2 participants were fatigue (n=4), anxiety (n=3), akathisia (n=2), somnolence (n=2), suicidal ideation (n=2), and suicide attempt (n=2).

[c]As reported in ≥10% of all participants.

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

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(f) 913-451-6409
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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.

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.

This letter and the enclosed material are provided in response to your unsolicited medical information inquiry. Please feel free to contact Neurocrine Medical Information at (877) 641-3461 or medinfo@neurocrine.com if you would like to request additional information.

References:

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Clinicaltrials.gov. NCT04102579.
3. Furr Stimming E, Claassen DO, Kayson E, et al. 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. Lancet Neurol. 2023;22(6):494-504.
4. Clinicaltrials.gov. NCT04400331.
5. Furr-Stimming E, et al. HSG 2023; Phoenix, AZ.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. INGREZZA Important Safety Information