(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real San Diego, CA 92130
http://www.neurocrinemedical.com/

Data for INGREZZA® (valbenazine) 60 mg Capsules

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding data on valbenazine 60 mg capsules.

INGREZZA® (valbenazine) capsules is indicated in adults for the treatment of tardive dyskinesia (TD) and for the treatment of chorea associated with Huntington's disease (HD).[1]

The INGREZZA FDA-approved Full Prescribing Information states the following regarding dosage and administration[1]:

> Administer INGREZZA orally with or without food.
>
> Tardive Dyskinesia
>
> The initial dosage for INGREZZA is 40 mg once daily. After one week, increase the dose to the recommended dosage of 80 mg once daily. A dosage of 40 mg or 60 mg once daily may be considered depending on response and tolerability.
>
> Chorea Associated with Huntington's Disease
>
> The initial dosage for INGREZZA is 40 mg once daily. Increase the dose in 20 mg increments every two weeks to the recommended dosage of 80 mg once daily. A dosage of 40 mg or 60 mg once daily may be considered depending on response and tolerability.

Tardive Dyskinesia

The U.S. Food and Drug Administration (FDA) approved a 60 mg INGREZZA (valbenazine) capsule dosing option in addition to the approved 40 mg and 80 mg dosing options for the treatment of adults with TD. Under the FDA's model-informed drug development (MIDD) pilot program (formalized by the FDA in 2018), the efficacy of 60 mg was assessed quantitatively through exposure-response (E-R) modeling and simulation analysis using data from KINECT 3®, a double-blind, randomized, placebo-controlled, pivotal Phase 3 study for the use of valbenazine 40 mg and 80 mg in patients with moderate-to-severe TD.[1-3]

The E-R model simulated 1,000 clinical trials of 2,000 participants (randomized 1:1:1:1 to placebo, valbenazine 40 mg, valbenazine 60 mg, or valbenazine 80 mg) to predict efficacy, as measured by Abnormal Involuntary Movement Scale (AIMS) dyskinesia total score change from baseline to Week 6. The simulation data set was designed to replicate the study design, dose regimen, and covariate distributions of the observed dataset for KINECT 3. The predicted population mean change in AIMS dyskinesia total score from baseline to Week 6 for valbenazine 60 mg dose was -2.69 (95% confidence interval [CI]: -3.30 to -2.13), which is within the efficacy range for valbenazine 40 mg and 80 mg once daily.[1-3]

The following information was added to the FDA-approved Full Prescribing Information as of April 2021[1]:

> **CLINICAL STUDIES**
>
> Efficacy of INGREZZA 60 mg
>
> Based on modeling and simulation, the predicted mean change from baseline in the AIMS dyskinesia total score at Week 6 for INGREZZA 60 mg once daily in subjects with TD is -2.69 (95% CI: -3.30, -2.13), which is within the efficacy range for INGREZZA 40 mg and 80 mg once daily.

(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real San Diego, CA 92130
http://www.neurocrinemedical.com/

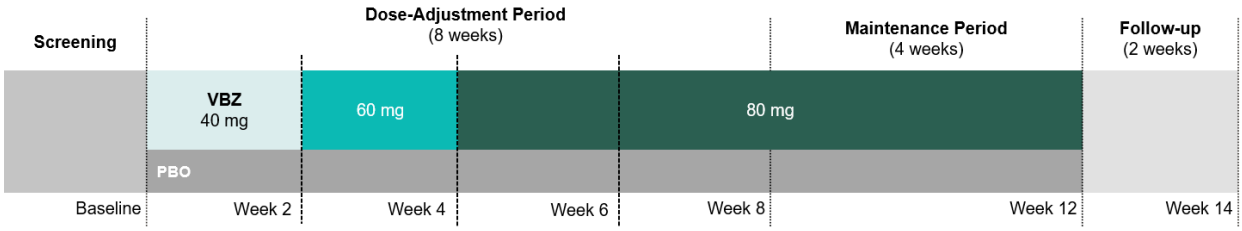
Chorea Associated with Huntington's Disease

KINECT®-HD was the the Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of valbenazine for the treatment of chorea associated with HD. Patients were randomized 1:1 to receive placebo (PBO) or valbenazine (VBZ).[4]

The study design included a 4-week screening period, 8-week dose-adjustment period, 4-week maintenance period, and a final follow-up visit 2 weeks after discontinuation of study drug (Figure 1). [4]

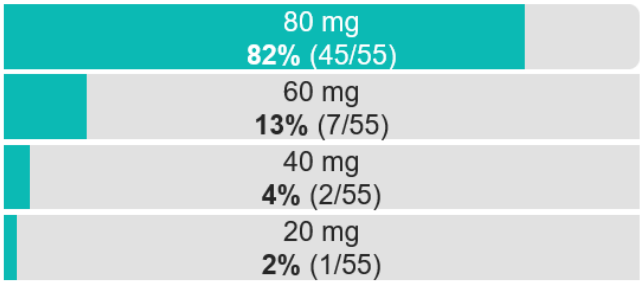
During the dose-adjustment period, valbenazine dosing started at 40 mg once daily with a planned dose escalation of 20 mg increases as tolerated at the end of weeks 2, 4, and 6 to a target dose of 80 mg once daily. Dose reductions were allowed at any time. During the maintenance period, the patient's dose was maintained and one dose reduction for tolerability was allowed. [4]

Figure 1: KINECT-HD Study Design[4]



Of the 128 patients randomized to treatment, 109 (85%) completed study treatment (55 receiving VBZ, 54 receiving PBO). Of the 55 patients who were treated with VBZ at the end of treatment (Week 12 visit), dosing was stratified as listed in Figure 2 below. [4]

Figure 2: Dose Stratification in KINECT-HD[4]

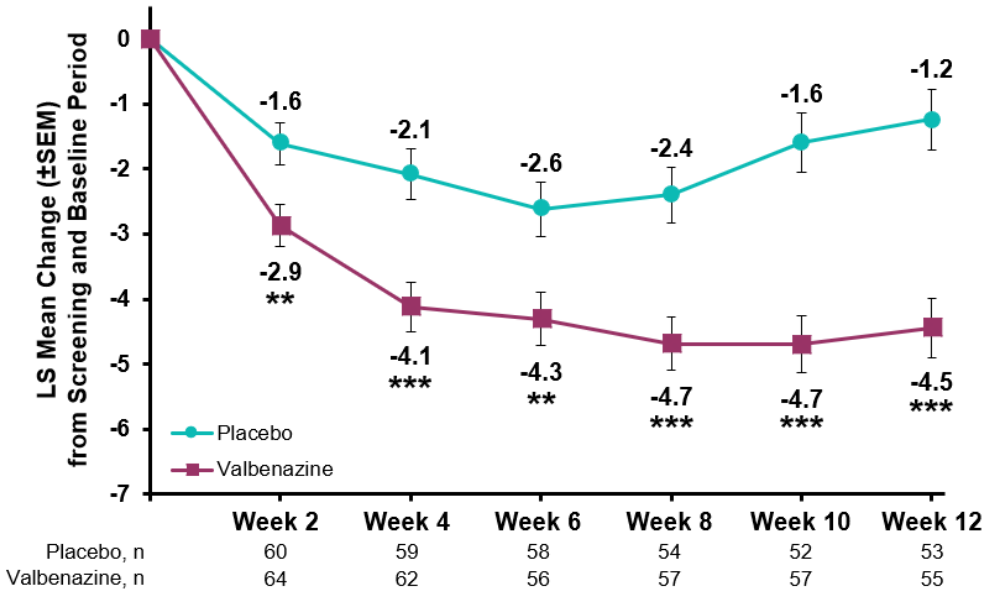


Additionally, a prespecified exploratory analysis of KINECT-HD was conducted to evaluate the Unified Huntington's Disease Rating Scale (UDHRS®) Total Maximal Chorea (TMC) score change, Clinical Global Impression of Change (CGI-C) response status, and Patient Global Impression of Change (PGI-C) response status (where response status was a score of 1="very much improved" or 2="much improved") at each post-baseline study visit.[5]

TMC score improvements from the screening and baseline period were significantly greater with VBZ vs PBO at all post-baseline visits. TMC score reductions with VBZ at Week 4 (after dose increase to 60 mg was allowed) was -4.1 (0.38), $p<0.001$ (Figure 3). [5]

(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real San Diego, CA 92130
http://www.neurocrinemedical.com/

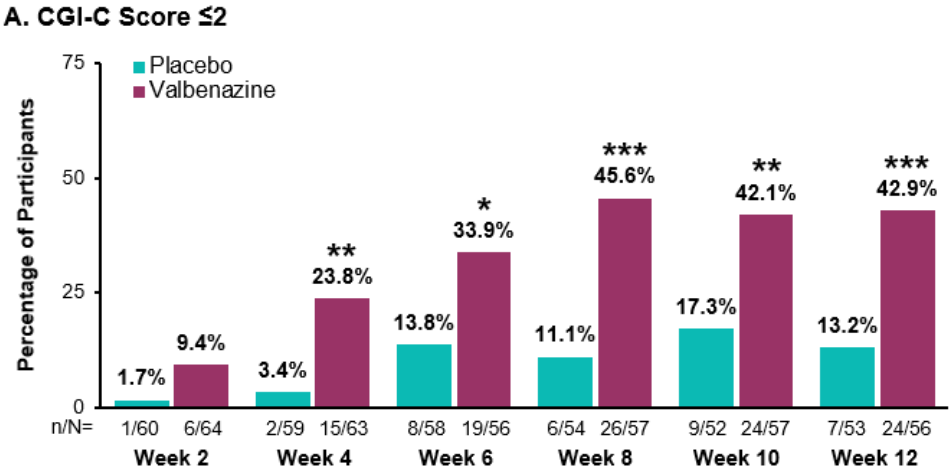
Figure 3: Mean Changes by Visit in UHDRS® TMC Scores[5]



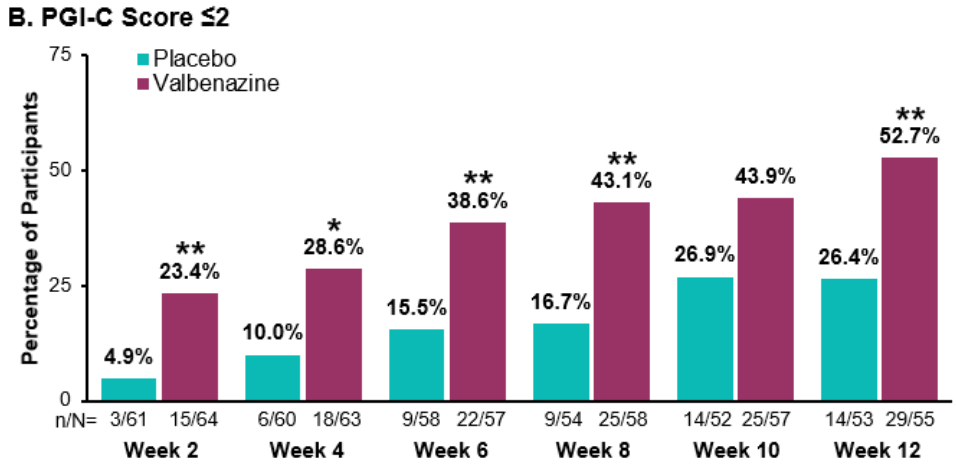
*P<0.05; **P<0.01; ***P<0.001 for valbenazine versus placebo (nominal significance).
LS, least-squares; SEM, standard error of the mean; TMC, total maximal chorea; UHDRS®, Unified Huntington's Disease Rating Scale.

At all post-baseline study visits, CGI-C and PGI-C responder rates were higher in the VBZ group than in the PBO group (Figure 4). A significant difference between treatment groups was first detected at Week 2 for PGI-C (with initial 40 mg dose) and Week 4 for CGI-C (after dose increase to 60 mg was allowed). [5]

Figure 4: CGI-C and PGI-C Responders by Visit[a,5]



(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real San Diego, CA 92130
http://www.neurocrinemedical.com/



[a]Responders were defined as participants with a score of 1 ("very much improved") or 2 ("much improved") on clinician-rated or self-rated change in chorea.
*P<0.05; **P<0.01; ***P<0.001 for valbenazine versus placebo (nominal significance).
CGI-C, Clinical Global Impression of Change; PGI-C, Patient Global Impression of Change.

The most common adverse reactions for valbenazine (≥5% and twice the rate of placebo) were somnolence/lethargy/sedation, urticaria, rash, insomnia.[1]

Adverse Reactions in KINECT-HD Reported at ≥4% and >Placebo[1]

	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%)

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.

(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real San Diego, CA 92130
http://www.neurocrinemedical.com/

References:

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Nguyen HQ, et al. A Model-Informed Drug Development Approach Supporting the Approval of a New Valbenazine Dose for Tardive Dyskinesia. Poster presented at the 2021 Annual Neuroscience Education Institute Congress; November 4-7, 2021; Colorado Springs, CO.
3. Data on File (VBZ-TD-0005). Neurocrine Biosciences, Inc.
4. 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.
5. Furr-Stimming E, et al. MDS 2023; Copenhagen, Denmark.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. Nguyen HQ, et al. A Model-Informed Drug Development Approach Supporting the Approval of a New Valbenazine Dose for Tardive Dyskinesia. Poster presented at the 2021 Annual Neuroscience Education Institute Congress; November 4-7, 2021; Colorado Springs, CO.