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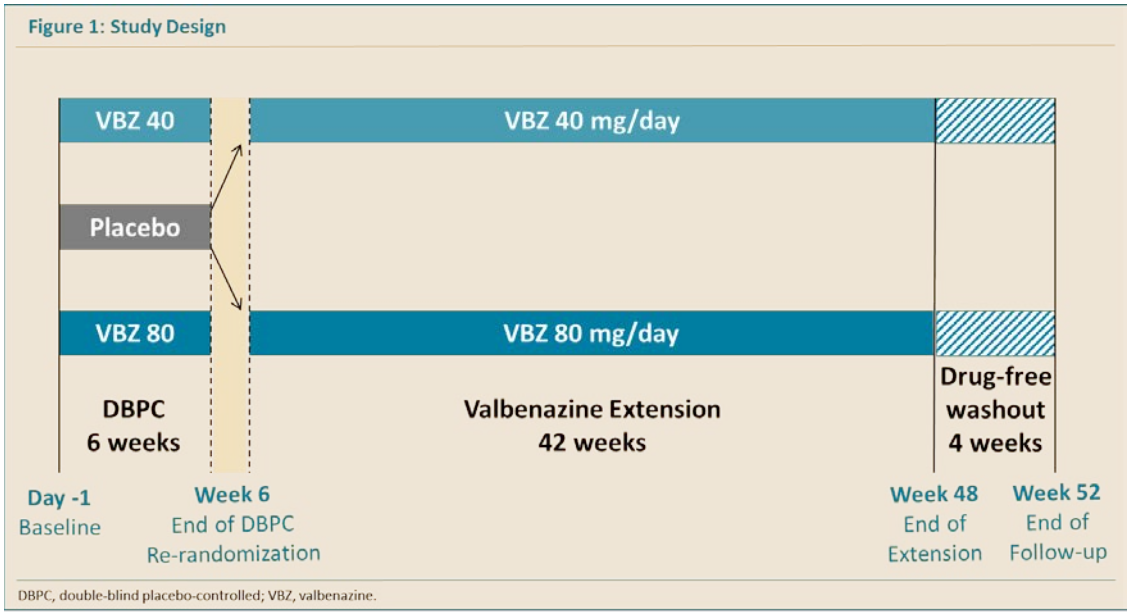
Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding long-term efficacy and safety data of INGREZZA® (valbenazine) capsules for the treatment of tardive dyskinesia (TD).

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.

KINECT 3: Phase III Double-blind VBZ Extension Period

KINECT 3, a randomized, double-blind, placebo-controlled (DBPC) Phase 3 study, was designed to assess the efficacy, safety and tolerability of VBZ in the treatment of TD. The primary efficacy endpoint was the mean change from baseline (CFB) at end of Week 6 in the Abnormal Involuntary Movement Scale (AIMS) dyskinesia total score (sum of Items 1-7) for VBZ 80 mg vs. placebo. AIMS scoring was based on the consensus of two blinded, central video AIMS raters. The key secondary efficacy endpoint is the Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) mean score at Week 6 for VBZ 80mg vs. placebo. Additional secondary endpoints included AIMS score CFB to Week 6 and CGI-TD score at Week 6 for VBZ 40mg vs. placebo.[1]



Subjects were eligible for the study if they were between the ages of 18 to 85 with a clinical diagnosis of schizophrenia or schizoaffective disorder with neuroleptic-induced TD or a mood disorder with neuroleptic-induced TD for at least 3 months prior to screening, had moderate or severe symptoms of TD, and were both medically and psychiatrically stable. Subjects were excluded from the study if they had a comorbid movement disorder more prominent than TD, known history of substance abuse, violent or suicidal behavior, neuroleptic malignant syndrome, or prolonged QT syndrome. [1]

Of the 234 randomized subjects, 205 subjects completed the 6-week placebo-controlled treatment period. Demographics were similar across treatment groups (Table 1).

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Table 1: Baseline Characteristics (ITT Population)

	Placebo (N = 76)	**VBZ 40 mg (n = 70)**	**VBZ 80 mg (n = 79)**
Age, mean years (SD)	57 (10.5)	55 (8.6)	56 (10.1)
Male, n (%)	42 (55.3)	40 (57.1)	39 (49.4)
Schizophrenia/schizoaffective disorder, n (5)	50 (65.8)	46 (65.7)	52 (65.8)
AIMS score, mean (SD)	9.9 (4.3)	9.8 (4.1)	10.4 (3.6)

Subjects who completed the DBPC period continued on to a 42-week double-blind VBZ extension (VE) period and a 4-week follow-up (Figure 1). Those initially randomized to placebo were re-randomized 1:1 to VBZ 80 or 40 mg/day and those initially randomized to VBZ 80 or 40 mg/day continued at the same dose. Subjects re-randomized to the higher VBZ dose received 40 mg/day during the first week of the VE period. Outcomes assessed in the VE period included the AIMS score CFB to Week 48 and the CGI-TD score at Week 48. The CGI-TD ranges from 1 ("very much improved") to 7 ("very much worse"). As in the KINECT 3 DBPC phase, AIMS scoring was based on the consensus of two blinded, central video AIMS raters.[2]

Of the 205 subjects who completed the DBPC period, 198 (96.6%) entered the VE period (80 mg/day, n=101; 40 mg/day, n=97), 124 (62.6%) subjected completed the VE period, and 121 (61.1%) completed follow-up.[2]

At Week 48, mean changes from DBPC baseline were -4.8 and -3.0, respectively, for the VBZ 80 and 40 mg/day dose groups. An increase in mean AIMS scores from Week 48 (80 mg/day, 6.2; 40 mg/day, 6.8) to Week 52 (80 mg/day, 9.8; 40 mg/day, 8.4) was observed, indicating that TD symptoms returned towards baseline levels during the 4-week period following discontinuation of VBZ. The mean CGI-TD scores were 2.1 and 2.4, respectively, for the VBZ 80 and 40 mg/day groups. The mean CGI-TD scores at Week 52 (80mg, 3.5, 40 mg, 3.2) were higher than those at Week 48, suggesting TD was reverting towards baseline levels during the drug-free follow-up period.[2]

Of the 198 subjects included in VE period, 69.2% had $\geq$1 treatment-emergent adverse event (TEAE) and 14.6% had $\geq$1 serious adverse event. The most common reasons for discontinuation from the VE period were AEs (15.7%), withdrawal of consent (8.6%), and loss to follow-up (7.1%).[2]

Pooled Long-term Safety Data

A long-term exposure (LTE) safety analysis of pooled Phase 2 and 3 studies included VBZ-treated subjects from 3 studies; KINECT (NCT01688037: 50 mg/day, 6-week double-blind, placebo-controlled (DBPC) period, 6-week open-label treatment period); KINECT 3 (NCT02274558: 80 or 40 mg/day, 6-week DBPC period, 42-week double-blind extension period); KINECT 4 (NCT02405091: 80 or 40 mg/day, 48-week open-label treatment). The pooled LTE 80 mg group combined data from the 80mg/day arms in KINECT 3 and KINECT 4. The pooled LTE 40 mg group included subjects from the 40-mg/day groups in KINECT 3 and KINECT 4 as well as the 50-mg/day group from KINECT (including subjects who initially received 2 weeks of VBZ 100 mg/day).[3]

Subjects were included in the studies if they had a clinical diagnosis of schizophrenia, schizoaffective disorder or mood disorder with neuroleptic-induced TD for at least 3 months prior to screening and a Brief Psychiatric Rating Scale score <50 at screening, and had moderate or severe TD as qualitatively assessed by blinded, external reviewers using a video captured at screening. Subjects were excluded from the studies if they had an active, clinically significant, and unstable medical condition within 1 month prior to screening, comorbid movement disorder (e.g. parkinsonism, akathisia, truncal dystonia) that was more prominent than TD, or significant risk for active suicidal ideation, suicidal behavior, or violent behavior.

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All subjects were required to be psychiatrically stable prior to study entry and stable doses of concomitant psychiatric medications were allowed throughout the studies.[3]

Safety parameters included AEs, vital signs, electrocardiogram (ECG), and laboratory tests. Subjects were assessed for maintenance of psychiatric stability throughout the studies using the following scales: Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS) and Columbia-Suicide Severity Rating Scale (C-SSRS). All outcomes were analyzed descriptively.[3]

Overall, 430 subjects were included in the LTE safety population (KINECT, n=46; KINECT 3, n=220; KINECT 4, n=164). The mean duration of VBZ exposure in all subjects was 204 days (± 119 days); median duration was 225 days (range, 1-356 days). Demographics and patient disposition were similar between the pooled treatment groups.[3]

The overall incidence of TEAEs in the LTE safety population was 66.5%; discontinuations due to AEs was 14.7% with no apparent difference between dose groups. The most common TEAEs (80 and 40 mg, combined) were headache (7.7%), urinary tract infection (7.4%), somnolence (6.3%), and fatigue (5.1%). No notable ECG changes were found, including the 81% of subjects who were taking concomitant mediations with a known potential to prolong QT. Laboratory parameters were similar across treatment groups; no clinically relevant changes were identified, including liver function tests and metabolic parameters. Mean psychiatric scales scores generally remained stable in subjects with schizophrenia/schizoaffective disorder (PANS, CDSS) or mood disorder (YMRS, MADRS) during long-term VBZ treatment.[3]

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. S.A. Factor, R.A. Hauser, S. Siegert, G.S. Liang, C.F. O'Brien. KINECT 3: A randomized, double-blind, placebo-controlled phase 3 trial of Valbenazine (NBI-98854) for tardive dyskinesia [abstract]. Mov Disord. 2016;31(suppl 2).
2. Grigoriadis, D., Remington, G., Comella, C.L., et al. Efficacy of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia: Results of a Long-Term Extension Study (KINECT 3 Extension). Presented at the 55th Annual Meeting of the American College of Neuropsychopharmacology. December 4-8, 2016; Hollywood, Florida.
3. Remington, G., Comella, C.L., Grigoriadis, D., et al. Safety and Tolerability of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia: Results of Long-Term Exposure Data from Three Studies. Presented at the 55th Annual Meeting of the American College of Neuropsychopharmacology. December 4-8, 2016; Hollywood, Florida.

Enclosures:

A. INGREZZA [package insert]. Neurocrine Biosciences, Inc., San Diego, CA; April 2017
B. Important Safety Information. Neurocrine Biosciences, Inc., San Diego, CA; April 2017
C. Grigoriadis, D., Remington, G., Comella, C.L., et al. Efficacy of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia: Results of a Long-Term Extension Study (KINECT 3 Extension). Presented at the 55th Annual Meeting of the American College of Neuropsychopharmacology. December 4-8, 2016; Hollywood, Florida.
D. Remington, G., Comella, C.L., Grigoriadis, D., et al. Safety and Tolerability of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia: Results of Long-Term Exposure Data from Three Studies. Presented at the 55th Annual Meeting of the American College of Neuropsychopharmacology. December 4-8, 2016; Hollywood, Florida.

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