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Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the impact of of INGREZZA® (valbenazine) capsules on psychiatric stability.

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

KINECT 2: Phase II Study

KINECT 2 was a randomized, double-blind, placebo-controlled Phase 2 study that investigated the safety, tolerability and efficacy of VBZ 25 mg, 50 mg or 75 mg in the treatment of subjects with moderate to severe tardive dyskinesia. The primary efficacy endpoint was the change from baseline of Abnormal Involuntary Movement Scale (AIMS) total dyskinesia scores (items 1-7) at 6 weeks vs. placebo. Subjects were required to be psychiatrically stable to qualify for the study. A total of 102 subjects were randomized 1:1 to receive either placebo or VBZ, beginning at 25 mg once-daily, for 6 weeks followed by a 2-week washout.[1]

Subjects were assessed for psychiatric stability using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia psychopathology and Calgary Depression Scale for Schizophrenia (CDSS) for depression in schizophrenia, Young Mania Rating Scale (YMRS) for manic symptoms, and the Montgomery-Asberg Depression Rating Scale (MADRS) for depression in mood disorders. The Columbia Suicide Severity Rating Scale (C-SSRS) was also evaluated at baseline versus Weeks 2 through 8 to measure suicidal ideation and behavior. All safety scales were analyzed descriptively.[1]

The safety population in this study was comprised of 49 and 51 subjects in the placebo and VBZ groups, respectively. Baseline characteristics were similar between the two groups. Psychiatric rating scale scores generally remained stable from baseline to Week 6 for both the VBZ and placebo groups. The percentages of subjects with suicidal ideation as measured by the C-SSRS for VBZ vs. placebo were 5.9% vs. 2.0% (screening) and 5.9% vs. 0% (Weeks 2-8). The 3 subjects with suicidal ideation in the VBZ group during the study all had a lifetime history of suicidal ideation, 2 of which had reported suicidal ideation within 3 months prior to screening. No subjects reported suicidal behavior in either group.[1]

KINECT 3: Phase III Fixed-dose Study

KINECT 3 was a randomized, double-blind, placebo-controlled Phase 3 study that assessed 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 AIMS dyskinesia total score (sum of Items 1-7) for VBZ 80 mg vs. placebo. Subjects were required to be medically and psychiatrically stable. Subjects were excluded from the study if they had a comorbid movement disorder more prominent than TD, known history or substance abuse, violent or suicidal behavior, neuroleptic malignant syndrome, or prolonged QT syndrome. There were 234 male and female subjects randomized 1:1:1 to receive placebo, VBZ 40mg, or VBZ 80mg once daily for a 6 week period.[2]

Similar to the KINECT 2 study, subjects were assessed for psychiatric stability throughout the studies using the following scales: PANSS, CDSS, YMRS, MADRS and C-SSRS.[2]

The safety analysis included 227 subjects from the three treatment groups (placebo: n = 76, VBZ 40 mg: n = 72, VBZ 80 mg: n = 79). Demographics were similar across treatment groups. Mean psychiatric scale scores generally remained stable during the study. No safety signal was detected for suicidality based on treatment-emergent adverse events (TEAE) and C-SSRS responses.[2]

Pooled Long-term Safety Data

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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 excluded from the studies if they had significant risk for active suicidal ideation, suicidal behavior, or violent behavior. All subjects were required to be psychiatrically stable prior to study entry and stable doses of concomitant psychiatric medications were allowed throughout the studies. 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 subject disposition were similar between the pooled treatment groups.[3]

Subjects were assessed for maintenance of psychiatric stability using PANSS, CDSS, YMRS, MADRS and C-SSRS. All outcomes were analyzed descriptively. Pooled long-term exposure analyses from Phase 2 and Phase 3 studies demonstrated that mean psychiatric scale scores generally remained stable for the 80 mg/day and 40 mg/day treatment groups in subjects with schizophrenia/schizoaffective disorder (PANSS, CDSS) or mood disorder (YMRS, MADRS) during long-term VBZ treatment.[3]

The overall incidence of TEAEs in the LTE safety population was 66.5% and discontinuation 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%). A lifetime history of suicidal ideation or behavior was reported in 39.8% of all subjects, with 4.5% in 40 mg group and 4.8% in 80 mg group reporting suicidal ideation during study participation.[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. Lindenmayer JP, Josiassen RC, Burke J, et al. (2016, May). Psychiatric Stability Maintained in Tardive Dyskinesia Subjects Treated with Valbenazine (NBI-98854). Presented at the 2016 annual meeting of the American Psychiatric Association, Atlanta, Georgia.
2. Factor SA, Hauser RA, Siegert S, et al. (2016, June). KINECT 3: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Valbenazine (NBI-98854) for Tardive Dyskinesia. Presented at the 2016 annual meeting of the International Congress of Parkinson's Disease and Movement Disorders Society, Berlin, Germany.
3. Remington, G, Comella, CL, Grigoriadis, D, et al. (2016, December). Safety and Tolerability of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia: Results of Long-Term Exposure Data from Three Studies. Presented at the 2016 annual meeting of the American College of Neuropsychopharmacology, Hollywood, Florida.

Enclosures

A. INGREZZA [package insert]. Neurocrine Biosciences, Inc., San Diego, CA; 2017.
B. Important Safety Information. Neurocrine Biosciences, Inc., San Diego, CA; 2017.
C. Lindenmayer JP, Josiassen RC, Burke J, et al. (2016, May). Psychiatric Stability Maintained in Tardive Dyskinesia Subjects Treated with Valbenazine (NBI-98854). Presented at the 2016 annual meeting of the American Psychiatric Association, Atlanta, Georgia.

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D. Factor SA, Hauser RA, Siegert S, et al. (2016, June). KINECT 3: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Valbenazine (NBI-98854) for Tardive Dyskinesia. Presented at the 2016 annual meeting of the International Congress of Parkinson's Disease and Movement Disorders Society, Berlin, Germany.
E. Remington, G, Comella, CL, Grigoriadis, D, et al. (2016, December). Safety and Tolerability of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia: Results of Long-Term Exposure Data from Three Studies. Presented at the 2016 annual meeting of the American College of Neuropsychopharmacology, Hollywood, Florida.

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