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KINECT® 4 Study

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding information on INGREZZA® (valbenazine) capsules and INGREZZA® SPRINKLE (valbenazine) capsules and the KINECT 4 study.

INGREZZA and INGREZZA SPRINKLE are vesicular monoamine transporter 2 (VMAT2) inhibitors indicated for the treatment of adults with tardive dyskinesia.[1]

KINECT 4 (NCT02405091) is an open-label, long-term (48-week open-label treatment period and a 4-week drug-free follow-up period) phase 3 study to evaluate the safety and tolerability of valbenazine in adults with tardive dyskinesia (TD). Participants were included in the study if they had a clinical diagnosis of schizophrenia/schizoaffective or mood disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). Participants received a starting dose of once-daily valbenazine 40 mg, which was escalated to 80 mg at the end of Week 4 if both of the following criteria were met: Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) score of ≥3 (minimally improved to very much worse) and acceptable safety/tolerability with the 40 mg dose, based on investigator judgment. From Weeks 4 to 48, a decrease to 40 mg was allowed if the subject was unable to tolerate the dose increase (80→40 mg group). Participants who were unable to tolerate the 40 mg dose were discontinued from the study. Effectiveness was assessed using the Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1-7), based on consensus scoring by 2 blinded central AIMS video raters (at baseline, Week 8 [first visit after dose escalation] and Week 52 [first visit after treatment withdrawal]) and by the investigator or site rater (at each study visit). Safety assessments included treatment-emergent adverse events (TEAEs).[2]

Of the 163 participants included in the analyses, 149 participants reached the Week 8 visit (40 mg, n=33; 80 mg, n=105; 80/40 mg, n=11) and 103 participants reached the Week 48 visit (i.e., treatment completers; 40 mg, n=20; 80 mg, n=74; 80/40 mg, n=9). Baseline characteristics were similar across treatment groups. Mean baseline AIMS total scores by central video raters were 10.2 (40 mg), 10 (80 mg) and 9.3 (80'40 mg). AIMS results based on central video raters were as follows: mean changes from baseline (CFB) to Week 8 were -4.5 (40 mg), -3.5 (80 mg), and -4.9 (80'40 mg) and mean CFB to Week 52 were -1.8 (40 mg), -3.3 (80 mg), and +0.2 (80'40 mg). AIMS results based on site raters were as follows: mean CFB to Week 8 were -7.5 (40 mg), -5.4 (80 mg), and -7.4 (80→40 mg); mean CFB to Week 48 were -10.2 (40 mg), -11 (80 mg), and -7.2 (80→40 mg); and mean CFB to Week 52 were -3.8 (40 mg), -4.6 (80 mg), and -3.3 (80→40 mg). In summary, AIMS results based on investigator rating indicated sustained reductions in AIMS total score and a return toward baseline levels of dyskinesia after treatment withdrawal.[2,3]

Approximately two-thirds (64.7%) of participants reported ≥1 TEAE at any time during valbenazine treatment. One death occurred due to breast cancer (80 mg), judged by the investigator as not related to study drug. Based on the Columbia-Suicide Severity Rating Scale (C-SSRS), 6.7% of all participants had any suicidal ideation or behavior during the treatment period. From Week 4 to Week 48, the only TEAEs that occurred in ≥5% of all participants (combined dose groups) were urinary tract infection (8.5%) and headache (5.2%). Changes from baseline in vital signs, ECG parameters, and laboratory test values were generally small and not clinically significant.[2,3]

For a more complete description of these analyses, please see the attached manuscript and published in *Journal of Clinical Psychopharmacology* by Marder S R, et. al. and data presentation from the 2017 American College of Neuropsychopharmacology Annual Congress by Marder S R, et. al.

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.

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References

1. INGREZZA [package insert]. Neurocrine Biosciences, Inc., San Diego, CA.
2. Marder SR, et. al. KINECT 4: A phase 3, one-year, open-label trial of valbenazine in participants with tardive dyskinesia. Poster presented at the 2017 American College of Neuropsychopharmacology Annual Congress; December 3-7, 2017; Palm Springs, CA.
3. Marder SR, et. al. A phase 3, 1-year, open-label trial of valbenazine in adults with tardive dyskinesia. *Journal of Clin Pyschopharmacology*. November/December 2019 - Volume 39 - Issue 6 - p 620-627. doi: 10.1097/JCP.0000000000001111.

Enclosures:

A. INGREZZA [package insert]. Neurocrine Biosciences, Inc., San Diego, CA.
B. INGREZZA [Important Safety Information]. San Diego, CA: Neurocrine Biosciences, Inc.
C. Marder SR, et. al. KINECT 4: A phase 3, one-year, open-label trial of valbenazine in participants with tardive dyskinesia. Poster presented at the 2017 American College of Neuropsychopharmacology Annual Congress; December 3-7, 2017; Palm Springs, CA.
D. Marder SR, et. al. A phase 3, 1-year, open-label trial of valbenazine in adults with tardive dyskinesia. *Journal of Clin Pyschopharmacology*. November/December 2019 - Volume 39 - Issue 6 - p 620-627. doi: 10.1097/JCP.0000000000001111.