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The Effect of Underlying Psychiatric Disorder on Tardive Dyskinesia Response to INGREZZA® (valbenazine) Capsules

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the effect of underlying psychiatric disorder (schizophrenia/schizoaffective disorder or mood disorder) on tardive dyskinesia (TD) response to INGREZZA® (valbenazine) capsules.

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.[1]

The long-term use of valbenazine (VBZ) in participants with schizophrenia/schizoaffective disorder (SZD) or mood disorder (MD) were evaluated in multiple studies. Please refer to the brief summaries of the results below.

KINECT 3: Phase III Double-blinded 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 adults with TD. Participants who completed the DBPC period continued with a 42-week double-blind VBZ extension (VE) period and a 4-week drug-free follow-up period.[2] Data from the KINECT 3 study were analyzed post-hoc to evaluate the long-term effects of VBZ in adults with TD and SZD. The mean change from baseline in the Abnormal Involuntary Movement Scale (AIMS) total score was used to evaluate change in TD severity, with a decreased AIMS total score from baseline indicating improvement in TD. In participants with SZD, baseline AIMS mean scores, as assessed by blinded central raters, were 8.8 and 10.1, respectively, for the VBZ 40 and 80 mg/day dose groups. At Week 48, AIMS mean score changes from the DBPC baseline were -2.5 and -4.2, respectively, for the VBZ 40 and 80 mg/day dose groups. The mean AIMS score changes from baseline at Week 52 (during the 4-week period following discontinuation of VBZ) were -0.8 and -1.0 for the VBZ 40mg and 80 mg/day dose groups, respectively. At Week 48, the mean Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) scores, as assessed by site raters, were 2.4 and 2.2, respectively, for the VBZ 40 and 80 mg/day groups. The mean CGI-TD scores at Week 52 increased to 3.3 and 3.4 for the VBZ 40 and 80 mg/day groups, respectively.[3,4]

Data from the KINECT 3 study were analyzed post-hoc to evaluate the long-term effects of VBZ in adults with TD and MD. In participants with MD, baseline AIMS mean scores, as assessed by blinded central raters, were 11.4 and 10.9, respectively, for the VBZ 40 and 80 mg/day dose groups. At Week 48, the AIMS mean score changes from DBPC baseline were -4.2 and -5.8, respectively, for the VBZ 40 and 80 mg/day dose groups. The mean AIMS scores changes from baseline at Week 52 were -2.7 and -1.6 for the VBZ 40 and 80 mg/day dose groups, respectively. At Week 48, the mean CGI-TD scores, as assessed by site raters, were 2.2 and 2.0, respectively, for the VBZ 40 and 80 mg/day groups. The mean CGI-TD scores at Week 52 increased to 2.8 and 3.6 for the VBZ 40 and 80 mg/day groups, respectively.[5,6]

During the VE period (post-Week 6 to Week 48), 69.2% of all participants (SZD and MD) had ≥ 1 treatment-emergent adverse event (TEAE). TEAEs reported in ≥ 5% of participants on VBZ 40 mg or 80 mg, respectively, were headache (7.2%; 6.9%), urinary tract infection (6.2%, 6.9%), diarrhea (3.1%, 7.9%), dizziness (4.1%, 6.9%), suicidal ideation, (5.2%, 5.0%), and depression (6.2%, 2.0%). There were no clinically important changes in clinical laboratory, vital signs, or ECG parameters during the VE or drug-free periods.[2]

KINECT 4: Phase III, Open-label, Long-term Study

KINECT 4 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 VBZ in adults with TD. Data from KINECT 4 were analyzed post-hoc to evaluate the long-term effects of VBZ in adults with TD and SZD or MD. As with KINECT 3, the mean change from baseline in the AIMS total score was used to evaluate change in TD severity, with a decreased AIMS total score from baseline indicating improvement in TD. In the SZD group, baseline AIMS mean scores, as assessed by site raters, were 14.4 and 14.7, respectively, for the VBZ 40 and 80 mg/day dose groups. Additionally, baseline AIMS mean scores for participants in the MD group were 13.1 and 15.7, respectively, for the VBZ 40 and 80 mg/day dose

groups. At Week 48, AIMS mean score change from baseline, as assessed by site raters, were as follows for the SZD group: VBZ 40 mg (n=14): -10.1; 80 mg (n=52): -10.7. For participants in the MD group at Week 48, AIMS mean score change from baseline were as follows: VBZ 40mg (n=6): -10.2; 80 mg (n=22): -11.6. The AIMS mean score change from baseline to Week 52 (end of drug-free period), as assessed by site raters, were as follows for participants in the SZD group: VBZ 40mg: -5.1; 80mg: -3.8. The AIMS mean score change from baseline to Week 52 for the MD participants were as follows: VBZ 40mg: -0.7; 80mg: -6.6.[7]

Discontinuation due to TEAEs occurred more frequently in the SZD subgroup (18%) than the MD subgroup (7%). TEAEs reported in ≥10% of participants in the MD subgroup were urinary tract infection (18.2%) and headache (15.9%). No TEAEs were reported in ≥10% of participants in the SZD subgroup. Psychiatric status remained stable from baseline to Week 48 in both subgroups: SZD (Positive and Negative Syndrome Scale [PANSS] positive, -0.7; PANSS negative, -0.6; Calgary Depression Scale for Schizophrenia [CDSS], -0.7); MD (Montgomery-Åsberg Depression Scale [MADRS], -0.3; Young Mania Rating Scale [YMRS], -0.3). Most participants (95%) had no change in the Columbia-Suicide Severity Rating Scale (C-SSRS) score during the study. In participants with no suicidal ideation at baseline (C-SSRS score=0), >90% continued to have no suicidal ideation throughout the study (baseline to Week 52): SZD, 95.7%; MD, 93.0%. Of the 5 participants who had suicidal ideation at baseline (C-SSRS score=1 to 3), none had any worsening during the study.[7]

1506: Phase IIIb, Long-Term, Open-Label, Rollover Study

The open-label, rollover study included participants who completed KINECT 3 or KINECT 4 (48 weeks of treatment and 4 weeks of drug-free period). Following the 4-week drug-free period of KINECT 3 and KINECT 4, participants who enrolled in the rollover study may have had an additional drug-free period. The mean duration of additional off-drug prior to rollover study start was 66.4 days (range, 0 to 324 days). Participants in the rollover study received treatment for up to 72 weeks or until VBZ became commercially available. Data from the rollover study were analyzed post-hoc to further assess the long-term safety and tolerability of once-daily VBZ in adults with TD and SZD or MD. The percentage of participants in the SZD group with a Clinical Global Impression of Severity-TD (CGIS-TD) score ≤2 ("normal, not at all ill" or "borderline ill"; assessed by site raters) at baseline were 8.7% (n=2/23) and 14.7% (n=11/75) for the VBZ 40 mg and 80mg/day groups, respectively. The percentages of participants in the MD group with a CGIS-TD score ≤2 at baseline were 0% (n=0/12) and 24.4% (n=10/41) for the VBZ 40 mg and 80mg/day groups, respectively. At Week 48, the percentage of participants with a CGIS-TD score ≤2 were as follows for the SZD group: VBZ 40mg: 37.5% (n=3/8); VBZ 80 mg: 60.9%(n=14/23). Additionally, Week 48 percentages of MD participants with a CGIS-TD score ≤2 were as follows: VBZ 40mg: 50.0% (n=2/4); VBZ 80mg: 93.8% (n=15/16). At baseline, 99.0% (n=103/104) of all SZD participants and 98.2% (n=55/56) of all MD participants had a Patient Satisfaction Questionnaire (PSQ) score ≤2 ("very satisfied" or "somewhat satisfied" with their prior VBZ experience; assessed by site raters). At Week 48, 97.1% (n=33/34) of the SZD subgroup and 100% (n=22/22) of the MD subgroup had a PSQ score ≤2.[8]

During treatment initiation (40 mg for 4 weeks), 6.7% of all SZD participants and 14.3% of all MD participants had any TEAE. Discontinuation due to a TEAE was reported in none of the SZD participants and 3.6% of all MD participants. From Week 4 to the end of study, less than 7% of all participants in either subgroup (SZD or MD) discontinued due to TEAEs. Based on available C-SSRS data, 99.0% (n=103/104) of the SZD subgroup and 94.6% (n=53/56) of the MD subgroup had no suicidal ideation at baseline (score=0). 99.0% (n=102/103) of the SZD subgroup and 96.2% (n=51/53) of the MD subgroup continued to have no emergence of suicidal ideation at any time during the rollover study. Among participants who had some suicidal ideation at baseline (score=1 to 3), none had any worsening in C-SSRS score at any time during treatment. Furthermore, there were no clinically important changes in laboratory parameters, vital signs, or ECG parameters.[8]

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]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Factor SA, et al. The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. *J Clin Psychiatry*. 2017 Nov/Dec;78(9):1344-1350.
3. Kane JM, et al. Long-Term Effects of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and Schizophrenia or Schizoaffective Disorder. Poster presented at the annual meeting of The College of Psychiatric and Neurologic Pharmacists; April 22-26, 2017; Phoenix, AZ.
4. Kane JM, et al. Efficacy of Valbenazine (NBI-98854) in Treating Subjects with Tardive Dyskinesia and Schizophrenia or Schizoaffective Disorder. Poster presented at the annual meeting of the American Psychiatric Association; May 20-24, 2017; San Diego, CA.
5. Correll CU, et al. Long-Term Effects of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and Mood Disorder. Poster presented at the annual meeting of The College of Psychiatric and Neurologic Pharmacists; April 22-26, 2017; Phoenix, AZ.
6. Correll CU, et al. Efficacy of Valbenazine (NBI-98854) in Treating Subjects with Tardive Dyskinesia and Mood Disorders. Poster presented at the annual meeting of the American Psychiatric Association; May 20-24, 2017; San Diego, CA.
7. Lindenmayer JP, et al. Long-Term Valbenazine Treatment in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder and Tardive Dyskinesia. Poster presented at the annual meeting of the American Psychiatric Association; May 5-9, 2018; New York, NY.
8. Grigoriadis D, et al. Long-Term Effects of Valbenazine on Tardive Dyskinesia in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder: Results from an Open-Label, Rollover Study. Poster presented at the American College of Neuropsychopharmacology annual meeting; December 9-13, 2018; Hollywood, FL.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

B. Kane JM, et al. Long-Term Effects of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and Schizophrenia or Schizoaffective Disorder. Poster presented at the annual meeting of The College of Psychiatric and Neurologic Pharmacists; April 22-26, 2017; Phoenix, AZ.

C. Kane JM, et al. Efficacy of Valbenazine (NBI-98854) in Treating Subjects with Tardive Dyskinesia and Schizophrenia or Schizoaffective Disorder. Poster presented at the annual meeting of the American Psychiatric Association; May 20-24, 2017; San Diego, CA.

D. Correll CU, et al. Long-Term Effects of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and Mood Disorder. Poster presented at the annual meeting of The College of Psychiatric and Neurologic Pharmacists; April 22-26, 2017; Phoenix, AZ.

E. Correll CU, et al. Efficacy of Valbenazine (NBI-98854) in Treating Subjects with Tardive Dyskinesia and Mood Disorders. Poster presented at the annual meeting of the American Psychiatric Association; May 20-24, 2017; San Diego, CA.

F. Lindenmayer JP, et al. Long-Term Valbenazine Treatment in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder and Tardive Dyskinesia. Poster presented at the annual meeting of the American Psychiatric Association; May 5-9, 2018; New York, NY.

G. Grigoriadis D, et al. Long-Term Effects of Valbenazine on Tardive Dyskinesia in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder: Results from an Open-Label, Rollover Study. Poster presented at the American College of Neuropsychopharmacology annual meeting; December 9-13, 2018; Hollywood, FL.