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The Effect of Age on Tardive Dyskinesia Outcomes in Patients Taking INGREZZA® (valbenazine) capsules

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the effect of age on tardive dyskinesia (TD) outcomes in patients taking INGREZZA® (valbenazine) capsules.

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

The INGREZZA FDA-approved Prescribing Information states that "No dose adjustment is required for elderly patients. In 3 randomized, placebo-controlled studies of INGREZZA, 16% were 65 years and older. The safety and effectiveness were similar in patients older than 65 years compared to younger patients."[1]

Pooled Double-blind, Placebo-controlled (DBPC), 6-week Studies

The effects of age (≥55 to 85 years or 18 to <55 years) on TD treatment outcomes were analyzed using pooled data from three 6-week, randomized, DBPC studies (two Phase 2 and one Phase 3): KINECT (NCT01688037), KINECT 2 (NCT01733121), and KINECT 3 (NCT02274558), respectively. The mean change from baseline (CFB) to Week 6 in the Abnormal Involuntary Movement Scale (AIMS) total score was used to evaluate TD improvement (lower AIMS total score indicates less overall TD severity). Interpretation of these post-hoc analyses may be limited due to small sample size.[2]

In the pooled analysis, the 40 mg valbenazine dose group included participants who received 50 mg from KINECT (including the arm that initially received 100mg for 2 weeks), 50 mg from KINECT 2, and 40 mg from KINECT 3. The 80 mg valbenazine dose group included participants on 75 mg from KINECT 2, and 80 mg from KINECT 3. Participants in KINECT 2 who received 25 mg of valbenazine were excluded.[2]

The pooled DBPC population (n=427) included 249 participants in the ≥55 to 85 years subgroup (80 mg, n=69; 40 mg, n=77; placebo [PBO], n=103) and 178 participants in the 18 to <55 years subgroup (80 mg, n=43; 40 mg, n=60; PBO, n=75). Across the two age subgroups (18 to <55 years, ≥55 to 85 years), the older subgroup had fewer men (60.1%, 56.2%), more white participants (48.9%, 61.8%), and a greater TD severity (AIMS total score, mean ± SD: 8.9 ± 4.0, 9.3 ± 4.3). The age subgroups were similar in terms of psychiatric diagnosis (schizophrenia: 73.6%, 73.1%), psychiatric symptomatology (Brief Psychiatric Rating Scale total score, mean ± SD: 31.1 ± 8.0, 30.4 ± 7.2), and recent history of suicidality (prior 3 months: 3.4%, 4.0%).[2]

For participants ≥55 to 85 years, the mean CFB to Week 6 in AIMS total score were greater for valbenazine (VBZ) (80 mg, -3.4; 40 mg, -2.6) than PBO (-0.4).For participants 18 to <55 years, the mean CFB to Week 6 in AIMS total score were also greater for VBZ (80 mg, -3.0; 40 mg, -2.1) than PBO (-1.0). [2]

Adverse reactions in the three placebo-controlled studies of 6-week duration reported at an incidence of >2% and greater than PBO were somnolence (10.9% and 4.2%), anticholinergic effects (5.4% and 4.9%), balance disorders/falls (4.1% and 2.2%), headache (3.4% and 2.7%,), akathisia (2.7% and 0.5%), vomiting (2.6% and 0.6%), nausea (2.3% and 2.1%) and arthralgia (2.3% and 0.5%), for VBZ and PBO, respectively.[1] The incidence of TEAEs were generally similar

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between VBZ and PBO in both age subgroups, with no individual TEAE occurring ≥ 5% of older VBZ-treated participants.[2]

Pooled Data from Two Phase 3, Long-term Studies

The effects of age (≥55 to 85 years or 18 to <55 years) on long-term TD treatment outcomes were analyzed using pooled data from two, Phase 3 studies: KINECT 3 Extension, a blinded extension study, and KINECT 4 (NCT02405091), a long-term open-label study. Both studies were 48-weeks in duration and included a 4-week, drug free, washout period (52-week total duration).[2]

In pooled long-term population, the 40 mg valbenazine dose group included participants on 40mg throughout KINECT 3 (DBPC and extension) and 40 mg from KINECT 4 (no dose escalation). The 80 mg valbenazine dose group included participants on 80 mg throughout KINECT 3 (DBPC and extension) and 80 mg from KINECT 4 (with dose escalation at week 4). Participants in KINECT 3 or KINECT 4 who had a dose reduction from 80 to 40 mg were included in the 80 mg group. KIENCT 3 participants who initially received placebo and KINECT 4 participants who had no post-week 4 assessment were excluded.[2]

The CFB to Week 48 (end of treatment) in the AIMS total score was used to evaluate long-term efficacy in younger (18 to <55 years) and older (≥55 to 85 years) participants. The pooled efficacy population (n=179) included 116 participants in the ≥55 to 85 years subgroup (80 mg, n=83; 40 mg, n=33) and 63 participants in the 18 to <55 years subgroup (80 mg, n=42; 40 mg, n=21) at the end of treatment (Week 48). The pooled efficacy population did not have a PBO comparison group.[2]

Mean improvements in AIMS total score were observed in both doses and age subgroups from baseline to Week 48 (end of treatment), with no significant difference between the younger and the older subgroups. In the older age subgroup, mean improvements in AIMS from baseline to Week 48 were -9.2 for the 80 mg group and -6.5 for the 40 mg group. For the younger age subgroup, mean AIMS improvements from baseline to Week 48 were -7.2 in the 80 mg group and -6.4 in the 40 mg group. Some loss of improvement was found at Week 52 in both age subgroups (≥55 to 85 years: 80mg, -3.2; 40mg, -3.1; 18 to <55 years: 80mg, -2.6; 40mg, -0.6).[2]

Phase 3b, Long-term Rollover Study

The effects of age (≥55 to 85 years or 18 to <55 years) on long-term TD treatment outcomes were analyzed in 1506, an open-label, rollover Phase 3b study (NCT02736955) that included participants who completed KINECT 3 or KINECT 4 (48 weeks of treatment and 4 weeks of drug-free washout 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, 1 to 324 days). Participants in the rollover study received treatment for up to 72 weeks or until VBZ became commercially available. Few participants reached Week 60 (n=4) and none reached Week 72 because valbenazine became commercially available before reaching those visits. All rollover study participants received once-daily VBZ 40 mg for 4 weeks. At Week 4, dosing was escalated to 80 mg based on tolerability and clinical assessment of TD. A dose reduction to 40 mg was allowed after Week 4 if 80 mg was not tolerated (80/40 mg dose group), and participants unable to tolerate 40 mg were discontinued from the study. All outcomes were analyzed descriptively in participants who received ≥1 dose of valbenazine and had any available post-baseline assessment.[3]

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Though the primary objective of this study was to further assess the long-term safety and tolerability of valbenazine, the CFB to Week 48 in the Clinical Global Impressions of Severity-TD (CGIS-TD: range, 1 “normal, not at all ill” to 7 “extremely ill”) score was used to evaluate long-term efficacy in younger (18 to <55 years) and older (≥55 to 85 years) participants. Mean CGIS-TD scores were summarized at every 12-week visit in each age subgroup. Interpretation of these post-hoc analyses may be limited due to small sample size.[4]

The pooled efficacy population (n=160) included 109 participants in the ≥55 to 85 years subgroup (80 mg, n=81; 40 mg, n=22; 80/40 mg, n=6) and 51 participants in the 18 to <55 years subgroup (80 mg, n=36; 40 mg, n=13; 80/40 mg, n=2) at the end of treatment (Week 48). Baseline characteristics were generally similar across treatment groups and age groups. In the younger subgroup, mean baseline CGIS-TD scores were 5.0, 3.8, and 3.4 in the 40mg, 80mg, and 80/40mg dose groups, respectively. In the older subgroup, mean baseline CGIS-TD scores were 4.1, 3.9, and 4.0 for the 40 mg, 80 mg, and 80/40 mg dose groups, respectively.[4]

In the younger age subgroup, the CGIS-TD mean score at Week 48 improved to 3.5, 2.4, and 3.3 in the 40 mg, 80 mg, and 80/40mg dose groups, respectively. In the older age subgroup, the CGIS-TD mean score at Week 48 improved to 2.3, 2.1, and 2.7 in the 40 mg, 80 mg, and 80/40mg dose groups, respectively. [4]

Long-term Safety

Data from the pooled long-term population (KINECT 3 and KINECT 4), and the rollover population were utilized to assess long-term safety in older (≥55 to 85 years) and younger (18 to <55 years) subgroups. This pooled long-term safety population and the rollover population included all participants who received ≥1 dose of study drug. Valbenazine dose groups (40 mg and 80 mg) were pooled for each population. Safety was analyzed descriptively, except for the treatment-emergent adverse event (TEAE) summary (chi-square test comparing age subgroups). Descriptive safety analysis included: Calgary Depression Scale for Schizophrenia (CDSS), Positive and Negative Syndrome Scale (PANSS), Montgomery-Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) in the pooled long-term population, and the Columbia-Suicide Severity Rating Scale (C-SSRS) for both the pooled long-term population and the rollover population.[5]

The pooled long-term population (n=383) included 239 participants in the ≥55 to 85 years subgroup and 144 participants in the 18 to <55 years subgroup. The rollover population (n=160) included 109 participants in the ≥55 to 85 years subgroup and 51 participants in the 18 to <55 years subgroup.[5]

In the pooled long-term population, there was a significantly higher percentage of participants from the ≥55 to 85 years subgroup vs. the 18 to < 55 years subgroup who experienced “any TEAE” (77.8% vs. 64.6%; P<0.01), “any serious TEAE” (19.2% vs. 10.4%; P<0.05), and “any TEAE leading to discontinuation” (19.7% vs. 11.8%; P<0.05). Headache was the most common TEAE in both the older subgroup (9.6%) and younger subgroup (8.3%).[5]

In the rollover population, there was no significant difference between the percentage of participants from the ≥55 to 85 years subgroup vs. the 18 to <55 years subgroup who experienced “any TEAE” (53.2% vs. 52.9%, p>0.05), “any serious TEAE” (10.2% vs. 9.8%, p>0.05), and “any TEAE leading to discontinuation” (3.7% vs. 9.8%). Somnolence was the most common TEAE in the older subgroup (4.6%), and cough was the most common TEAE in the younger subgroup (9.8%).[5]

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In the pooled long-term population, the mean change in psychiatric scale scores for schizophrenia (PANSS and CDSS) and mood (MADRS, and YMRS) generally remained stable in both age subgroups.[5]

Most participants had no suicidal ideation at baseline (i.e., C-SSRS) and continued to have no emergence of suicidal ideation at any time during the long-term studies (18 to <55 years, 93.5%; ≥55 to 85 years, 92.7%) or the rollover study (18 to <55 years, 100%; ≥55 to 85 years, 97.2%). Among participants who had some suicidal ideation at baseline (i.e., C-SSRS score=1 to 3), none had a worsening in C-SSRS score at any time during treatment.[5]

For a more complete description of these analyses, please see the enclosed data presentations.

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. INGREZZA [package insert]. Neurocrine Biosciences, Inc., San Diego, CA.
2. Sajatovic M, et al. The effects of valbenazine on tardive dyskinesia in older and younger patients. Int J Geriatr Psychiatry. 2020 Jan; 35(1): 69-79.
3. Lindenmayer JP, et al. A long-term, open-label study of valbenazine for tardive dyskinesia. CNS Spectrums. 2020:1-9.
4. Sajatovic M, et al. Global improvements in tardive dyskinesia and patient satisfaction with valbenazine in older and younger patients: results from an open-label, rollover study. Poster presented at the American Association of Geriatric Psychiatry; March 1-4, 2019; Atlanta, GA.
5. Alexopoulous GS, et al. Long-term valbenazine studies in younger and older adults with tardive dyskinesia. Poster presented at the American Association of Geriatric Psychiatry; March 1-4, 2019; Atlanta, GA.

Enclosures:

A. INGREZZA [package insert]. Neurocrine Biosciences, Inc., San Diego, CA.
B. Sajatovic M, et al. Global Improvements in Tardive Dyskinesia and Patient Satisfaction with Valbenazine in Older and Younger Patients: Results from an Open-Label, Rollover Study. Poster presented at the American Association of Geriatric Psychiatry; March 1-4, 2019; Atlanta, GA.
C. Alexopoulous GS, et al. Long-term valbenazine studies in younger and older adults with tardive dyskinesia. Poster presented at the American Association of Geriatric Psychiatry; March 1-4, 2019; Atlanta, GA.

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