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The Effects of INGREZZA® (valbenazine) Capsules and INGREZZA® SPRINKLE (valbenazine) Capsules Across Body Regions in Patients with Tardive Dyskinesia

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the effects of INGREZZA and INGREZZA SPRINKLE across body regions.

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

The effect of INGREZZA and INGREZZA SPRINKLE on tardive dyskinesia (TD) across body regions was evaluated using post-hoc analysis of abnormal involuntary movement scale (AIMS) item scores from the KINECT® 3 (NCT02274558), KINECT® 3 extension period, and KINECT® 4 studies (NCT02405091).

KINECT 3 Double-Blind Placebo-Controlled (DBPC) Study and Extension Period

KINECT 3 is a 6-week randomized, DBPC, Phase 3 study to assess the efficacy, safety, and tolerability of valbenazine (VBZ) for the treatment of adults with 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. Participants who completed the KINECT 3 DBPC period continued to a 42-week double-blind VBZ extension (VE) period (Week 48) and a 4-week drug-free washout period (Week 52).[2]

Mean scores for AIMS items 1-7 (7 different body regions: face, lips/ perioral, jaw, tongue, upper extremities, lower extremities, and trunk) were analyzed descriptively at baseline and at each study visit, in participants who had available assessments. AIMS was scored by a pair of expert central AIMS video raters (neurologists specializing in movement disorders), who were blinded to treatment and study visit sequence. Category shifts for AIMS items 1-7 (i.e. AIMS Shift) were defined as an improvement from a score of ≥3 (moderate/severe rating) at baseline to score ≤2 (none/minimal/mild rating) at Weeks 6 (end of DBPC period), Week 48 (end of VE period), and Week 52 (end of drug-free washout period). AIMS shift data at Week 6 were analyzed using the Cochran-Mantel-Haenszel test to compare each VBZ dose to placebo, while AIMS shift data at Week 48 and Week 52 were analyzed descriptively.[2]

Of the participants in the DBPC population who had available assessments at baseline and Week 6, the number in any treatment group with at least 1 baseline AIMS item score ≥ 3 was as follows: face (n=16, lips/perioral (n=36), jaw (n=60), tongue (n=57), upper extremities (n=15), lower extremities (n=14), and trunk (n=28).[2]

At Week 6, the percentage of participants who met the AIMS shift criteria was significantly greater with VBZ versus placebo in the jaw (both doses), tongue (both doses), lips/perioral (VBZ 80 mg), and trunk (VBZ 40 mg), $P<0.05$ vs. placebo. At Week 48, 50% of participants in both dose groups met the AIMS shift criteria in all 7 body regions. At Week 52, the percentage of participants meeting AIMS shift criteria generally decreased.[2]

The most common treatment-emergent adverse events (TEAEs) for VBZ (both dosage groups combined) and placebo in the KINECT 3 study were somnolence (5.3% and 3.9%, respectively), akathisia (3.3% and 1.3%, respectively), and dry mouth (3.3% and 1.3% respectively), while suicidal ideation was the most common in the placebo group (5.3% compared with 2.6% in the VBZ groups combined).[3] The most common TEAEs for VBZ (both dosage groups combined) in the VE period were headache (7.1%) and urinary tract infection (6.6%).[4]

For a more complete description of these analyses, please see attached data presentation from the 2018 Parkinson Study Group annual meeting & symposium by Singer, et al.[2]

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KINECT 4 Open-label, Long-term Study

KINECT 4 (NCT02405091) is an open-label, long-term, phase 3 study (48-week open-label treatment period and a 4-week drug-free washout period) to evaluate the safety and tolerability of VBZ in adults with TD.[5]

AIMS was scored at baseline, Week 48 (end of treatment), and Week 52 (after 4-week washout) by site raters (i.e., investigators or other trained and qualified individuals). Clinically meaningful changes across body regions (i.e. AIMS Shift) were defined as an improvement from a score of ≥3 (moderate/severe rating) at baseline to a score of ≤2 (none/minimal/mild rating) after treatment (Week 48) or washout (Week 52). Due to the nature of the descriptive analysis in the KINECT 4 study, there was no placebo comparison group.[5]

Of all participants (combined VBZ 40 mg and 80 mg groups) who had available assessments at baseline, Week 48, and Week 52, the number in any treatment group with at least 1 baseline AIMS score ≥3 was as follows: lips/perioral (n=63), tongue (n=59), jaw (n=51), upper extremities (n=50), face (n=41), lower extremities (n=29), and trunk (n=26). At the end of treatment (Week 48), 100% of all participants had an AIMS shift in the following regions: lips/perioral, upper extremities, and lower extremities. Further, 98% of all participants had an AIMS shift in the face, jaw, and tongue regions. At Week 52, some loss of effect was seen, as AIMS shift rates of all participants decreased across all items, see **Table 1**.[5]

Table 1. Participants Meeting Shift Criteria at Weeks 48 and 52

Shift, n/N (%)	Body Region (AIMS Items 1-7)						
	Face	Lips/ perioral	Jaw	Tongue	Upper Extremities	Lower Extremities	Trunk
At Week 48							
Valbenazine 40 mg	9/9 (100)	6/6 (100)	10/10 (100)	11/11 (100)	8/8 (100)	5/5 (100)	7/8 (88)
Valbenazine 80 mg	28/29 (97)	53/53 (100)	38/38 (100)	44/45 (98)	40/40 (100)	22/22 (100)	16/18 (89)
All Participants[a]	40/41 (98)	63/63 (100)	50/51 (98)	58/59 (98)	50/50 (100)	29/29 (100)	23/26 (89)
At Week 52[b]							
Valbenazine 40 mg	5/9 (56)	2/6 (33)	5/10 (50)	3/11 (27)	5/8 (63)	1/5 (20)	4/8 (50)
Valbenazine 80 mg	17/29 (59)	32/53 (60)	21/38 (55)	20/45 (44)	20/40 (50)	14/22 (64)	10/18 (56)
All Participants[a]	23/41 (56)	36/63 (57)	26/51 (51)	26/59 (44)	27/50 (54)	17/29 (59)	14/26 (54)

[a]Includes the 11 participants who had a dose reduction from 80 to 40 mg after Week 4.[b] After a 4-week washout.

The most common treatment-emergent-adverse events (TEAEs) for VBZ reported in ≥ 5% of all participants (n=153) in the KINECT 4 study were urinary tract infection (8.5%) and headache (5.2%). One death occurred due to breast cancer in a patient on VBZ 80 mg and was judged by the investigator as not related to the study drug. [6]

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For a more complete description of these analyses, please see attached data presentation from the 2018 International Congress of Parkinson's Disease and Movement Disorders annual meeting by Comella, et al.[5]

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]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Singer C, et al. Effects of once-daily valbenazine by body region in subjects with tardive dyskinesia. Poster presented at the Parkinson Study Group; May 4-6, 2018; Jersey City, NJ.
3. Hauser RA, et al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. American Journal of Psychiatry. 2017; 174:5,476-484.
4. 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.
5. Comella CL, et al. Effects of long-term valbenazine on tardive dyskinesia by body region: shift analyses of KINECT 4 study results. Poster presented at the International Congress of Parkinson's Disease and Movement Disorders; October 5-9, 2018; Hong Kong, China.
6. 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 American College of Neuropsychopharmacology annual meeting; December 3-7, 2017; Palm Springs, CA.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. INGREZZA [Important Safety Information]. San Diego, CA: Neurocrine Biosciences, Inc.
C. Singer C, et al. Effects of once-daily valbenazine by body region in subjects with tardive dyskinesia. Poster presented at the Parkinson Study Group; May 4-6, 2018; Jersey City, NJ.
D. Comella CL, et al. Effects of long-term valbenazine on tardive dyskinesia by body region: shift analyses of KINECT 4 study results. Poster presented at the International Congress of Parkinson's Disease and Movement Disorders; October 5-9, 2018; Hong Kong, China.