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Meta-Analysis of Randomized Controlled Trials of INGREZZA® (valbenazine) and AUSTEDO® (deutetrabenazine) Efficacy for Treatment of Adults with Tardive Dyskinesia

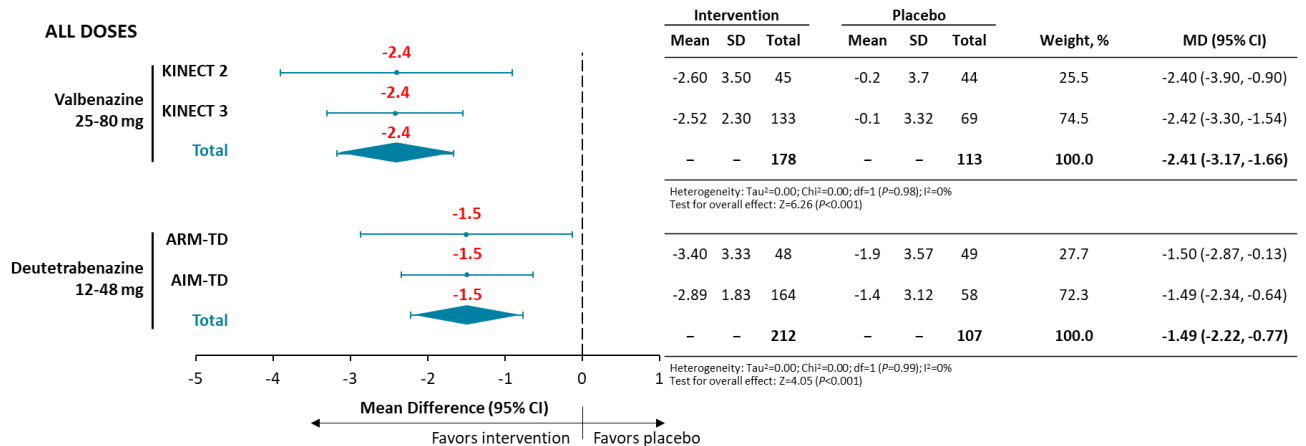
Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the meta-analysis of randomized controlled trials of valbenazine and deutetrabenazine efficacy for treatment of adults with tardive dyskinesia.

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia (TD).<sup>1</sup>

A systematic literature search was used to first find all randomized controlled trials (RCTs) for valbenazine (VBZ) and deutetrabenazine (DTBZ) used for the treatment of tardive dyskinesia (TD).<sup>2</sup> Efficacy outcomes including mean Abnormal Involuntary Movement Scale (AIMS) change from baseline (CFB) and AIMS response (defined as a  $\geq 50\%$  improvement from baseline) were evaluated in pooled comparisons using inverse variance method for AIMS CFB, and odds ratios (ORs) estimated using Mantel-Haenszel test for AIMS response. No safety outcomes were included in this analysis. Four studies were found in the literature search, ARM-TD and AIM-TD for deutetrabenazine, and KINECT-2 and KINECT-3 for valbenazine.<sup>3-6</sup> For the ARM-TD trial AIMS response was not reported and was estimated from visual inspection of a 2016 poster.<sup>7</sup> Along with overall pooled outcomes sensitivity analyses were conducted in subgroups of pooled low and high dosage groups (VBZ high dose=80mg, low dose=40mg; DTBZ high dose=36mg, low dose=24mg). For the flexible-dose studies that did not report results by dose (i.e., KINECT 2 and ARM-TD), outcomes for the entire population were used for both high- and low-dose subgroups.<sup>3,5</sup>

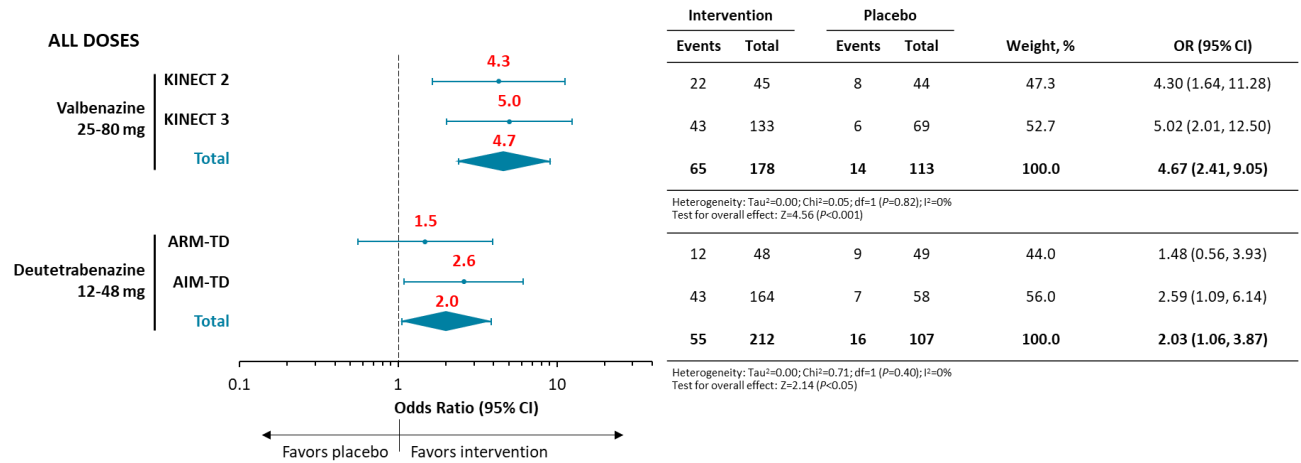
For AIMS CFB, the mean difference from placebo indicated statistically significant improvements with VBZ (all doses, -2.41;  $P < 0.001$ ) and DTBZ (all doses, -1.49;  $P < 0.001$ ) (Figure 1). Moreover, Analyses of AIMS response indicated significantly better outcomes with VBZ (all doses, OR=4.67;  $P < 0.001$ ) and DTBZ (all doses, OR=2.03;  $P < 0.05$ ) versus placebo.

Figure 1: AIMS Mean Score Change from Baseline (All Doses)



In sensitivity analyses for high and low-dose subgroups (VBZ high dose=80mg + entire KINECT 2 population, low dose=40mg + entire KINECT 2 population; DTBZ high dose=36mg + entire ARM-TD population, low dose=24mg + entire ARM-TD population), AIMS CFB showed statistical significance for VBZ high dose (-2.85; P<0.001), VBZ low dose (-2.01; P<0.001), DTBZ high dose (-1.74; P<0.001), and DTBZ low dose (-1.67; P<0.001). However, sensitivity analyses for AIMS  $\geq$ 50% improvement from baseline showed significance for VBZ high dose (OR=5.49; P<0.001) and low dose (OR=3.79; P<0.001), but not for DTBZ high dose (OR=2.29; P=0.06) or low dose (OR=2.39; P=0.07).

**Figure 2:  $\geq$ 50% AIMS Improvement From Baseline (All Doses)**



**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](mailto:medinfo@neurocrine.com) if you would like to request additional information.**

**References:**

1. INGREZZA® (valbenzazine) prescribing information. Neurocrine Biosciences, Inc.; San Diego, CA. August 2018.
2. Aggarwal S et al. Meta-Analysis of Randomized Controlled Trials of Valbenzazine and Deutetrabenazine Efficacy for Treatment of Tardive Dyskinesia. Poster presented at the 2018 Academy of Managed Care Pharmacy Nexus Meeting, Orlando, FL.
3. Fernandez HH, Factor SA, Hauser RA, et al. Randomized controlled trial of deutetrabenazine for tardive dyskinesia: the ARM-TD study. *Neurology*. 2017;88:2003-2010.
4. Anderson KE, Stamler D, Davis MD, et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind randomized, placebo controlled, phase 3 trial. *Lancet Psychiatry*. 2017;4(8):595-604
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7. Jimenez-Shahed J, Factor SA, Ondo WG, et al. Deutetrabenazine is Associated with an Improvement in Involuntary Movements in Patients with Tardive Dyskinesia (TD) as Seen by the High Proportion of Responders to Treatment in the ARM-TD Study. Poster presented at the 29<sup>th</sup> U.S. Psychiatric and Mental Health Congress, 2016, San Antonio, Texas.

Enclosures:

1. Aggarwal S et al. Meta-Analysis of Randomized Controlled Trials of Valbenazine and Deutetrabenazine Efficacy for Treatment of Tardive Dyskinesia. Poster presented at the 2018 Academy of Managed Care Pharmacy Nexus Meeting, Orlando, FL.