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The Effects of Valbenazine in Participants with Tardive Dyskinesia: Results of the 1-Year KINECT 3 Extension Study

Factor SA, Remington G, Comella CL, et al. *J Clin Psychiatry.* 2017;78(9):1344-1350.[a]

[a] Supplementary section of article not provided as part of this reprint.

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BACKGROUND

Tardive dyskinesia (TD) is a chronic and potentially irreversible drug-induced movement disorder.[1] TD is associated with prolonged exposure associated with exposure to dopamine receptor blocking agents (DRBAs), including first-generation (typical) and second-generation (atypical) antipsychotics.[2,3]

- Even with the advent of second-generation antipsychotics, 20% to 30% of patients with prolonged exposure to DRBAs develop TD[4]
- Dose reduction or discontinuation of the offending antipsychotic is often not effective without exacerbation of the psychiatric disorder[5]

Valbenazine, a novel selective VMAT2 inhibitor, is an FDA-approved treatment indicated for adults with TD. In a pivotal, phase 3 study (KINECT 3), valbenazine 80 mg showed significant improvements in TD severity at 6 weeks and had a generally well-tolerated safety profile.[6]

VMAT2, vesicular monoamine transporter.

STUDY OBJECTIVE

The KINECT 3 extension period evaluated the long-term safety and tolerability of once-daily valbenazine (40 mg or 80 mg) in adults with TD. In addition, long term effects were assessed for once daily (40 mg or 80mg) valbenazine treatment in adults with TD.[7]

METHODOLOGY

In the KINECT 3 study, eligible patients received 6 weeks of once-daily valbenazine (40 mg or 80 mg) or placebo.[6,b] Consenting patients who completed the 6-week DBPC study were then entered into the blinded extension period, and randomized to receive either valbenazine 40 mg or 80 mg once daily. During the first week of the extension period, all randomized patients received valbenazine 40 mg once daily. After the first week, patients who were randomized to receive valbenazine 80 mg once-daily had their dose increased.[7,c]

DBPC, double-blind, placebo-controlled.

[b] In the 6-week study, the primary efficacy endpoint was change in AIMS dyskinesia score (sum of items 1-7) from baseline to week 6 for valbenazine 80 mg once daily vs placebo.[6]

[c] Those already receiving either valbenazine dose continued the same dose, while those receiving placebo were randomized (1:1) to valbenazine 40 mg or 80 mg once daily. Participants were allowed 1 dose reduction during the study with blinding maintained.[7]

Safety Analyses[7,d]

- Treatment-emergent adverse events (TEAEs)
- Psychiatric status
- Treatment-emergent akathisia or parkinsonism
- Emergence of suicidal ideation or behavior
- 12-lead electrocardiogram (ECG)
- Vital signs and laboratory assessments

[d] Safety population.[6,7]

Efficacy measures assessed[8,e,f]

- Mean Abnormal Involuntary Movement Score (AIMS) change from baseline
- Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD)
- Patient Global Impression of Change (PGIC)

[e] Intent-to-treat population.[6,7]

[f] Analyzed at each postbaseline visit. In the extension study, baseline was defined as Week 8.[7]

STUDY POPULATION

In the extension study, valbenazine was studied in a broad population of patients with various underlying diagnoses and treatment regimens. All participants had stable psychiatric status at baseline.[7,g]

[g] Based on the following accepted measurement scales: Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS).[7]

Key Inclusion Criteria[6,7]	Select Study Demographics[7]

• Medically stable adults
• 18 to 85 years of age
	• 198 (96.6%) participants from the DBPC study entered the extension period
	  ○ 124 (62.6%) participants completed the extension period[i]
	  ○ 121 (61.1%) completed washout and week 52 follow-up visit

• Participants had one of these diagnoses
  ○ Schizophrenia
  ○ Schizoaffective disorder
  ○ Mood disorder
	• 64.4% had a diagnosis of schizophrenia or schizoaffective disorder
	• 35.6% had mood disorder

• Diagnosis of DRBA-induced TD[h] • Qualitative assessment of moderate to severe TD	• 71.2% of participants were taking second-generation (atypical) antipsychotics • 7.9% were taking first-generation (typical) antipsychotics

[h] According to the DSM IV, ≥3 months prior to screening.[6]

[i] Treatment-emergent adverse events leading to study discontinuation in >2 participants were somnolence (80 mg once daily, n=3) and suicidal ideation (80 mg once daily, n=1; 40 mg once daily, n=2). These cases of suicidal ideation or behavior/attempt all resolved with hospitalization/medical management, and were judged by the site investigators as unlikely related to valbenazine.[7]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

QT Prolongation

INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Please see additional Important Safety Information throughout and full Prescribing Information in inside pocket.

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SAFETY PROFILE

In the extension period, valbenazine was generally well tolerated in a population of patients with diagnosed schizophrenia, schizoaffective disorder, or mood disorder.[7]

Treatment-emergent adverse events ≥5% in either valbenazine treatment group[7,j,k]

- Headache (7.1%)
- Urinary tract infection (6.6%)
- Diarrhea (5.6%)
- Dizziness (5.6%)
- Suicidal ideation (5.1%)
- Depression (4.0%)

[j] Safety population.[6,7]
[k] Combined valbenazine 40 mg and 80 mg once-daily.[7]

There were no clinically important changes in clinical laboratory assessments, vital signs, or ECG parameters during the extension or washout periods.[7]

Psychiatric status generally remained stable during the extension study.[7]

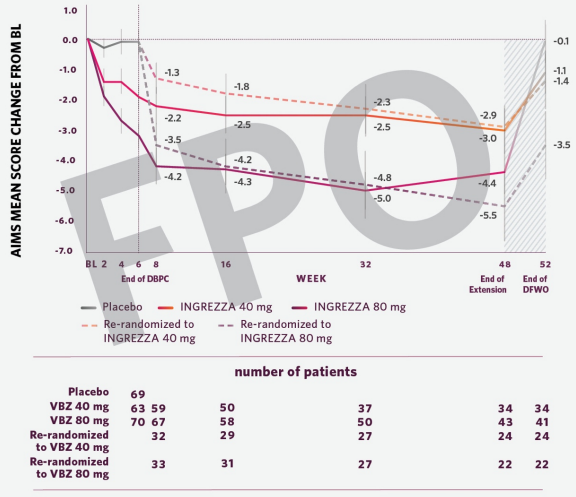
Long-term treatment with once-daily valbenazine may be an effective treatment for TD in adults with a range of presentations and treatment histories[7]

- Valbenazine was generally well tolerated through 48 weeks, with sustained improvements in TD
- TD symptoms tended to return to baseline during the washout period, supporting the maintenance efficacy of ongoing valbenazine treatment

LONG-TERM RESULTS

AIMS mean score showed sustained TD improvement through Week 48[10]

Extension study of INGREZZA 40 mg and INGREZZA 80 mg (ITT population)



number of patients

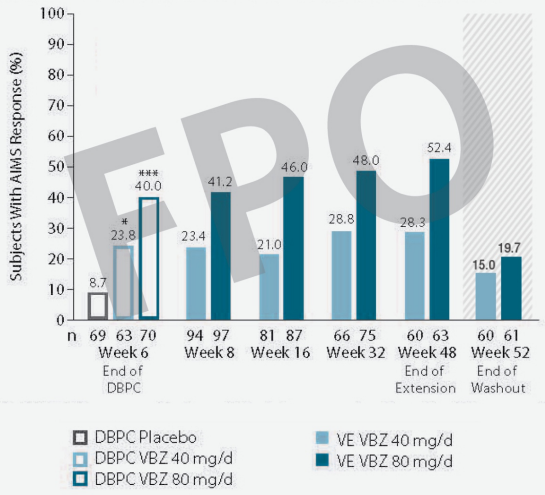
Placebo	69				
VBZ 40 mg	63	59	50	37	34	34
VBZ 80 mg	70	67	58	50	43	41
Re-randomized to VBZ 40 mg		32	29	27	24	24
Re-randomized to VBZ 80 mg		33	31	27	22	22

AT 48 WEEKS: **~39% TD reduction** with INGREZZA 80 mg

[k] See Figure 1B in enclosed reprint.
[l] In a post hoc analysis that included patients randomized to INGREZZA 80 mg at baseline and those who were re-randomized to INGREZZA 80 mg at Week 6.[11]
** *P*<.01 vs placebo; *** *P*<.001 vs placebo; †*P*<.01 vs baseline; §*P*<.001 vs baseline.
AIMS, Abnormal Involuntary Movement Scale; BL, baseline; DFWO, drug-free washout; ITT, intent-to-treat.

AIMS score improvement by ≥50% was generally consistent through Week 48[10]

Percentage of extension study participants with AIMS score improved ≥50%



[m] See Figure 3A in enclosed reprint.
[n] For AIMS response at week 6, the difference between each valbenazine group (80 and 40 mg once daily), and the placebo group was determined using a 2-sided Cochran-Mantel-Haenszel analysis. No statistical testing between valbenazine dose groups was conducted for the extension and washout periods.[11]
* *P*<.05 vs placebo; *** *P*<.001 vs placebo.

During the 4-week washout period, mean AIMS scores generally returned toward baseline[7]

- **Based on clinical assessment and need, continued valbenazine treatment may be required to maintain TD improvements**

For more information, please visit INGREZZAHCP.com

INGREZZA® (valbenazine) capsules

[BACK COVER]

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The most common adverse reaction (≥5% and twice the rate of placebo) is somnolence. Other adverse reactions (≥2% and >placebo) include: anticholinergic effects, balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see inside pocket for full Prescribing Information or visit www.INGREZZAHCP.com.

References: 1. Cloud LJ, Zutshi D, Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. *Neurotherapeutics.* 2014;11(1):166-176. **2.** Stahl SM. *Essential Psychopharmacology Online*. Based on: Stahl SM. *Stahl's Essential Psychopharmacology*. 4th ed. Cambridge, UK: Cambridge University Press;2013. http://stahlonline.cambridge.org/essential_4th_chapter.jsf?page=chapter5_introduction.htm&name=Chapter%205&title=Conventional%20antipsychotics #c02598-5-1. Accessed February 1, 2017. **3.** Sayers AC, Bürki HR, Ruch W, et al. Neuroleptic-induced hypersensitivity of striatal dopamine receptors in the rat as a model of tardive dyskinesia: effects of clozapine, haloperidol, loxapine and chlorpromazine. *Psychopharmalogia*. 1975;41(2):97-104. **4.** Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive dyskinesia prevalence in the period of second generation antipsychotic use: a meta-analysis. *J Clin Psychiatry*. 2017;78(3):e264-e278.

5. Soares KV, McGrath JJ. The treatment of tardive dyskinesia—a systematic review. *Schizophr Res.* 1999;39(1):1-16. **6**. Hauser RA, Factor SA, Marder SR, et al. KINECT 3: A phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry*. 2017;174(5):476-484. **7.** Factor SA, Remington G, Comella CL, et al. The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. *J Clin Psychiatry.* 2017;78(9):1344-1350. **8.** Data on file.

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