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PUBLIC ADVISORY COUNCIL

Project: Cost Effectiveness of Valbenazine and Deutetrabenazine for Tardive Dyskinesia

Model Analysis Plan

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APPROACH

The primary aim of this analysis is to estimate the cost-effectiveness of valbenazine and deutetrabenazine for the treatment of symptoms of moderate-to-severe tardive dyskinesia (TD) compared to no treatment. The model structure for this assessment is depicted below. The model will be developed in Microsoft Excel.

METHODS

Treatments

The interventions assessed in this model are as follows:

- Valbenazine (Neurocrine Biosciences, Inc.)
- Deutetrabenazine (Teva Pharmaceuticals, Inc.)
- No treatment

Patients not receiving active treatment for TD symptoms will be modeled using outcomes associated with the placebo arms from the relevant clinical trials. Note that, while other medications are used off-label for managing TD symptoms, these will not be included in our analyses, as the quality of evidence supporting their use in TD is greatly inferior to the clinical trial data available for valbenazine and deutetrabenazine. In addition, other strategies such as lowering the dose of the medication thought to be causing TD symptoms, will not be considered because of similar concerns with available evidence and the fact that such changes were not allowed in the study protocols for valbenzaine and deutetrabenazine.

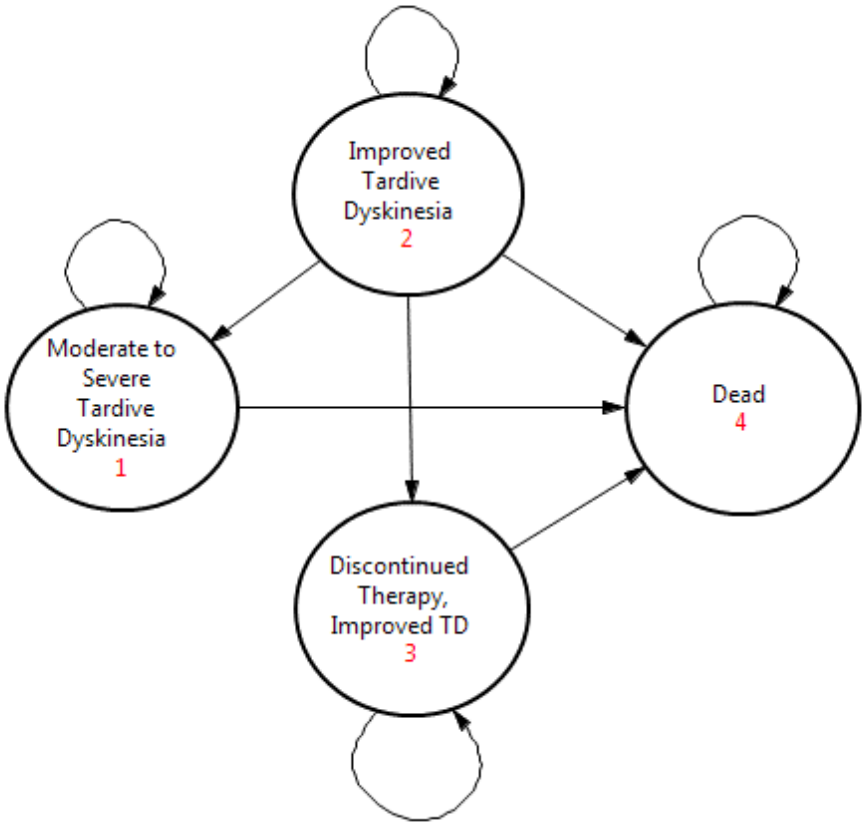
Overview and Model Structure

We will develop a new Markov model of patients with moderate to severe tardive dyskinesia in a representative population of U.S. adults aged 18 years and older with the underlying conditions of schizophrenia, schizoaffective disorders, and bipolar depression. Patient response will be based on improvements in Abnormal Involuntary Movement Scale (AIMS) scores observed in clinical trials. In the base-case model, as treatment effects were quite rapid in the trials and the overall model has annual cycles, patients will begin in either the “moderate to severe tardive dyskinesia” or the “improved tardive dyskinesia” health states. The proportion of patients starting in the “improved tardive dyskinesia” health state will be based on the proportion responding to therapy or placebo in clinical trials. In subsequent cycles, responders will remain in the “improved tardive dyskinesia” state until discontinuing therapy or dying. Each cycle, some patients will discontinue therapy due to adverse events. Those discontinuing therapy will primarily move to “moderate to severe tardive dyskinesia.” A smaller proportion will continue to move to “discontinued therapy, improved tardive dyskinesia” at a rate similar to those in the placebo arm of the clinical trials. The model will employ one-year cycles over a lifetime time horizon, modeling patients from treatment initiation until death. Mortality rates will be based on epidemiologic evidence of

mortality in patients with the underlying conditions of schizophrenia, schizoaffective disorders, and bipolar depression. It is assumed in the base case of the model that therapies for tardive dyskinesia do not affect mortality.

Base-case model inputs will include the probability of symptom improvement, utility gain from symptom improvement, and health care costs. We will use a U.S. health care system perspective (i.e., focus on direct medical care costs only) with a lifetime time horizon and a 3% discount rate for costs and health outcomes. Cost-effectiveness will also be estimated for shorter time horizons of one, two, and five years. One-way and probabilistic sensitivity analyses will be used to examine the effects of all inputs on the model. Special scenario analyses will also be conducted in bipolar and schizoaffective patients to incorporate potential indirect effects of improved TD on the underlying conditions in terms of costs and quality adjusted life years (see the scenario analysis section below). Threshold analyses will be used when there are insufficient data for potential model scenarios.

Figure 1. Markov model structure



Key Assumptions

We have made several assumptions for the base-case model, as follows:

Assumption	Rationale
Patient response to treatment is reflected in their initial health states	Cycles are annual and the response to treatment is rapid. Patients responding will be started in the "improved tardive dyskinesia" state, while those who do not respond will begin in the "moderate to severe tardive dyskinesia" state. This will prevent a lag in response to therapy that would occur if all patients were started in the "moderate to severe tardive dyskinesia" state.
All patients receiving treatment will incur one month of treatment costs as an initial cost.	Patients initiating therapy would have a trial period of the medications. Medications are usually dispensed in one-month increments.
Patients not responding to treatment with valbenazine or deutetrabenazine discontinue their treatment.	Patients not responding will not see benefits of therapy and should have no treatment costs.
Response to treatment remains constant for all responders. Patients do not improve beyond their initial response to therapy nor decline while remaining in the "improved tardive dyskinesia" state.	There is limited information on the individual change in response to therapy over time. Furthermore, there is no information on the impact of tardive dyskinesia severity on quality of life. It is necessary to assume that tardive dyskinesia impact on quality of life, as measured by a utility, will remain constant while patients are responding to therapy.
Discontinuation rates for valbenazine and deutetrabenazine are similar to those observed in clinical trials of these agents in the first cycle. Following the first cycle, discontinuation rates are constant and modeled based on the longest available time periods in data from the continuation phase of the trials. Patients responding to but subsequently discontinuing treatment are modeled the same as those	There is no information regarding discontinuation rates of therapies beyond the clinical trial extensions.

beginning with no treatment. Patients discontinuing therapy will enter either "moderate to severe TD" or "discontinued therapy with improved TD."	
Patients who respond to treatment will be assumed to have no added psychiatric and neurologist visit costs related to TD.	There is currently no data on the costs associated with treated tardive dyskinesia. It is likely that patients whose tardive dyskinesia has improved will incur fewer office visits. This is a conservative estimate biasing the results in favor of the therapies.
Utility gains associated with being in the "improved tardive dyskinesia" state, compared with being in the "moderate to severe tardive dyskinesia state" are equal to population estimates obtained assessing the incremental impact of having no tardive dyskinesia relative to having moderate to severe tardive dyskinesia.	There is limited data on the impact of tardive dyskinesia on utility and no data for varying severity of tardive dyskinesia. This assumption will result in maximal benefit to patients, biasing the model results in favor of the therapies.
Tardive dyskinesia and treatments do not have a direct effect on mortality.	Valbenazine and deutetrabenazine have not been demonstrated as having an impact on mortality. The scenario analysis will address the possibility that improved tardive dyskinesia may reverse a possible risk of increased mortality associated with having tardive dyskinesia seen in one study.[1]
Treatment of tardive dyskinesia has no effect on the outcomes or costs of treating the underlying conditions. However, these potential effects will be considered in scenario analyses.	Valbenazine and deutetrabenazine have not been shown to improve the management of underlying conditions. Although not evaluated in clinical trials, patient and pharmaceutical company stakeholders have suggested that such benefits are likely. Therefore, these potential indirect benefits of therapy will be modeled in scenario analyses.

Population

The population for this analysis will be patients with moderate to severe tardive dyskinesia in a representative population of US adults aged 18-64 years with the underlying conditions of schizophrenia, schizoaffective disorders, and bipolar depression. The proportion of patients with schizophrenia, schizoaffective disorders, and bipolar depression being treated with antipsychotic medications seen in US patient populations, namely 70.2% for schizophrenia and schizoaffective disorders and 29.8% for bipolar.[2]

Input Parameters

Population Demographics

The modeled population will be derived from statistics of the adult U.S. populations, aged 18-64 years, likely to develop tardive dyskinesia with the underlying conditions of schizophrenia, schizoaffective disorder, and bipolar disorder. Patients receiving metoclopramide for gastrointestinal conditions and developing tardive dyskinesia will not be modeled in this analysis due to the very small number of patients currently treated long-term, and substantial differences in the underlying demographics and other characteristics of these patients.

In the model, patients with schizophrenia or schizoaffective disorder will have a mean age of 38 years and be 52.5% female.[3] Patients with bipolar disorder will have a mean age of 40 years and be 64.8% female.[4] Note that the clinical trials of valbenazine and deutetrabenazine included a much higher proportion of male patients (66.4%). These estimates are consistent with a meta-analysis of clinical trials involving patients with tardive dyskinesia, where the mean age was 42.8 years.[5] The proportion of patients with bipolar will be 29.8% and the proportion with schizophrenia or schizoaffective disorder will be 70.2%. This implies an expected age of 39 years.

Initial Transition

Patients enter the model as having immediately improved or not, based on success rates with therapy or with no tardive dyskinesia treatment. For the base case, treatment effectiveness will be based on the proportion of patients having a ≥50% improvement in the AIMS score (with other measures of improvement such as CGI-TD and CGI-C being considered in sensitivity analyses) at the maximal tolerated dose from the clinical trials (80 mg for valbenazine and 36 mg for deutetrabenzine). The rationale for using the maximal dose is that in clinical practice, patients will be titrated to maximum medication effectiveness without intolerable side effects. In addition, the highest effect was seen at the maximal dose.

Those who have improved will enter the model in the “improved tardive dyskinesia” state. Those who have not will begin the model in the “moderate to severe tardive dyskinesia” state. The probabilities associated with starting in the improved tardive dyskinesia state will be primarily abstracted from phase III clinical trials and open-label extension trials evaluating response to valbenazine and deutetrabenazine compared with placebo.

Table 1. Proportion of patients starting in the "improved tardive dyskinesia" state for the initial distribution

Comparator	Improvement scale	Proportion who improved	Reference
Valbenazine versus placebo (6 weeks)	50% improvement in AIMS	Valbenazine 40 mg: 23.8% Valbenazine 80 mg: 40.0% Placebo: 8.7%	Hauser 2017[6]
Valbenazine open label (48 weeks)	50% improvement in AIMS	Valbenazine 80 mg: 52.4% Valbenazine 40 mg: 28.3%	Grigoriadis[7]
Valbenazine versus placebo (6 weeks)	50% improvement in AIMS	Valbenazine: 48.9% Placebo: 18.2%	O'Brien[8]
Valbenazine versus placebo (6 weeks)	CGI-TD responders (score ≤ 2)	Valbenazine 40 mg: 31.7%* Valbenazine 80 mg: 31.4%* Placebo: 20.3%* *Differences not significant	Grigoriadis[7]
Valbenazine versus placebo (6 weeks)	CGI-TD "much improved or very much improved"	Valbenazine: 67% Placebo: 16%	O'Brien[8]
Valbenazine open label (48 weeks)	CGI-TD responders (score ≤ 2)	Valbenazine 80 mg: 76.2% Valbenazine 40 mg: 59.0%	Grigoriadis[7]
Deutetrabenazine versus placebo (12 weeks)	50% improvement in AIMS	Deutetrabenazine 24 mg: Approx. 33% Deutetrabenazine 36 mg: Approx. 30% Placebo: Approx. 10%	Jimenez-Shahed[9]
Deutetrabenazine versus placebo (12 weeks)	CGI-C "improved or much improved"	Deutetrabenazine 24 mg: 49% Deutetrabenazine 36 mg: 44% Placebo: 26%	Anderson[10]
Deutetrabenazine versus placebo (12 weeks), combined ARM-TD and AIM-TD trials	CGI-C "improved or much improved"	Deutetrabenazine (unspecified dose): 48% Placebo: 30%	Fernandez[11]
Deutetrabenazine versus placebo (54 weeks)	CGI-C "improved or much improved"	Deutetrabenazine (unspecified dose): 72%	Anderson[12]
Deutetrabenazine versus placebo (12 weeks)	CGI-C "much improved or very much improved"	Deutetrabenazine (mean dose 38.3 mg/d): 48.2% Placebo: 40.4%	Fernandez[13]
Deutetrabenazine versus placebo (12 weeks)	PGIC "much improved or very much improved"	Deutetrabenazine (mean dose 38.3 mg/d): 45.8% Placebo: 28.6%	Fernandez[13]

Transition probabilities

Patients who initially respond but subsequently discontinue therapy will transition to the "discontinued therapy, improved tardive dyskinesia" state based on placebo response rates from the clinical trials, or to the "moderate to severe dyskinesia" state. [6, 7, 10, 12] Patients may also move to the absorbing state, death, based on mortality rates of the underlying conditions obtained from epidemiologic studies. Patients with improved tardive dyskinesia who continue to receive drug therapy and do not die will continue in the "improved tardive dyskinesia" state each cycle.

Mortality will be modeled using age- and gender-adjusted mortality estimates for the general population, obtained from the CDC/NCHS National Vital Statistics System, and further adjusted to reflect mortality rates in the underlying populations of schizophrenia, schizoaffective disorder,[14] and bipolar disorder.[15]

Costs

The model will include all costs associated with caring for tardive dyskinesia. These costs will include treatment costs, primary care physician visits, and specialist (i.e., neurologist and psychiatrist) visits associated with the management of moderate-to-severe tardive dyskinesia. Patients who do not respond to treatment will be assumed to discontinue therapy and therefore not incur additional TD-specific treatment costs. Patients with moderate to severe tardive dyskinesia will incur additional psychiatric and neurologist visit costs. Patients who respond to treatment will be assumed to have no additional psychiatric and neurologist visit costs. Patients with no treatment and improved symptoms of tardive dyskinesia will have no incremental costs assigned to them in the model. In addition, there are no costs associated with death in the model. Medicare fee schedules will be used to assign psychiatric and neurologist visit costs. Drug treatment costs will be based on industry-provided estimates if any, or will be based on benchmark discount levels for products in similar therapeutic areas to arrive at a net price.

Utilities

Utility estimates for patients in any health state in the model will reflect a weighted average of utilities for the underlying conditions. Gains in utility from improvement in tardive dyskinesia symptoms will be modeled based on utility estimates available in the literature of having moderate to severe tardive dyskinesia relative to not having tardive dyskinesia. The base-case will utilize a utility decrement (subtractive) of 0.095 to all patients remaining in the "moderate to severe tardive dyskinesia" state. Patients in the "improved tardive dyskinesia" or "discontinued therapy, improved tardive dyskinesia" states will not incur the disutility. The utility gained from improvement in tardive dyskinesia is assumed to be independent of any other underlying condition(s).

Table 2. Potential disutility values for patients with tardive dyskinesia.

Disutility or quality of life scale type	Disutility Value (SD)	Source
Standard gamble utility multiplier*	0.857 (0.825-0.888)	Lenert 2004[16]
Additive standard gamble disutility**	-0.095 (0.073-0.117)	Lenert 2004[16]
Additive disutility**	0.14 (N/A)	Wang 2004[17] Glennie 1997[18] Oh 2001[19]

*Patients with tardive dyskinesia will have their initial utility (i.e. without tardive dyskinesia) multiplied by the multiplicative utility to derive the final utility for their initial health state plus tardive dyskinesia.

**Patients with tardive dyskinesia will have the disutility for tardive dyskinesia added to their initial health state utility (i.e. without tardive dyskinesia) to derive the final utility.

Adverse Events

There were no severe adverse events noted in the clinical trials. However, discontinuation rates differed between the two treatments (and placebo) due to minor adverse events. The model will reflect these differential discontinuation rates from adverse events, but will not include costs or utilities related to adverse events, as these effects are assumed to be minimal. We do note that deutetrabenazine carries a black box warning for suicidal ideation based on data from its clinical trial program for Huntington's disease-associated movement disorders (the initial indication for the drug). As described above, the effects of possible excess mortality associated with TD will be assessed in sensitivity analyses.

Table 3. Potential inputs for discontinuation because of adverse events (AEs), by therapy and trial

Active treatment	Treatment rate	Placebo rate	Evaluation Period	Reference
Valbenazine (any event leading to discontinuation)	40 mg: 5.6% 80 mg: 6.3%	5.3%	6 weeks	Hauser 2017[6]
Valbenazine (AE leading to discontinuation)	40 mg: 3% 80 mg: 4%	3%	6 weeks	Factor 2017[20]
Valbenazine (AE leading to discontinuation)	40 mg: 16.0% 80 mg: 13.5%	14.7%	Mean 225 days	Remington[21]
Deutetrabenazine (AE leading to discontinuation)	1.7%	3.4%	12 weeks	Fernandez 2017[13]

Model Outcomes

The model will estimate the amount of time, on average, patients spend in each health state while on valbenazine, deutrabenazine, or no treatment. Utility-adjusted time spent in each health state will be summed to provide estimates of quality-adjusted life expectancy for each treatment arm.

Model outcomes of interest will include:

- By intervention:
    - Total costs (discounted)
    - Quality adjusted life expectancy (undiscounted and discounted)
    - Cost per case of improved tardive dyskinesia
- Pairwise comparisons:
    - Incremental cost-effectiveness ratios (cost/QALY) of each treatment versus usual care

Sensitivity Analyses

We will run one-way sensitivity analyses on all model inputs to identify the key drivers of model outcomes. Probabilistic sensitivity analysis will be performed by jointly varying model inputs over 5,000 simulations. Acceptability curves and other summary measures of variance will be generated and presented.

Scenario Analyses on Potential Indirect Effects of TD Treatment by Underlying Condition

We will conduct scenario analyses, taking into account the inclusion of potential indirect effects of valbenazine and deutetrabenazine on productivity[22] and adherence to antipsychotic and depression medications. In the first scenario analysis, potential productivity gains from improved tardive dyskinesia will be included in the base-case model for all patients responding to therapy. In additional scenario analyses, separate models will be developed for schizophrenia/schizoaffective disorders and bipolar disorder patients. The models will incorporate well controlled and poorly controlled mental health states for the underlying conditions. It has been hypothesized that improved tardive dyskinesia control results in better management of the underlying conditions. In these scenario analyses, treatment with valbenazine and deutetrabenazine will be modeled to impact the hypothesized improved management of schizophrenia/schizoaffective disorders and bipolar disorder, resulting in additional utility gains and reduced total costs. Given available data, we will perform threshold analyses, based on willingness-to-pay thresholds of $50,000 to $150,000 per QALY, determining the magnitude of indirect treatment effects on quality-adjusted life years gained, cost offsets, or productivity gains required for the treatment to be considered cost-effective.[23]

REFERENCES

1. Ballesteros J, Gonzalez-Pinto A, Bulbena A. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of seven independent studies. *Journal of clinical psychopharmacology.* 2000;20(2):188-194.

2. Domino ME, Swartz MS. Who are the new users of antipsychotic medications? *Psychiatric services.* 2008;59(5):507-514.

3. Carney CP, Jones L, Woolson RF. Medical comorbidity in women and men with schizophrenia: a population-based controlled study. *Journal of general internal medicine.* 2006;21(11):1133-1137.

4. Shippee ND, Shah ND, Williams MD, Moriarty JP, Frye MA, Ziegenfuss JY. Differences in demographic composition and in work, social, and functional limitations among the populations with unipolar depression and bipolar disorder: results from a nationally representative sample. *Health and quality of life outcomes.* 2011;9:90.

5. Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive Dyskinesia Prevalence in the Period of Second-Generation Antipsychotic Use: A Meta-Analysis. *The Journal of clinical psychiatry.* 2017;78(3):e264-e278.

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. *The American journal of psychiatry.* 2017;174(5):476-484.

7. Grigoriadis D, Comella CL, Remington G, Jimenez R, Burke J, O'Brien CF. Efficacy of valbenzine (NBI-98854) in subjects with tardive dyskinesia: Results of a long-term extension study (KINECT 3 extension). *55th Annual Meeting of the American College of Neuropsychopharmacology, Dec 4-8, 2016; Hollywood, FL.* 2016.

8. O'Brien CF, Jimenez R, Hauser RA, et al. NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: A randomized, double-blind, placebo-controlled study. *Movement disorders : official journal of the Movement Disorder Society.* 2015;30(12):1681-1687.

9. Jimenez-Shahed J, Fernandez HH, Stamler D, et al. Deutetrabenazine is associated with an improvement in involuntary movements in patients with tardive dyskinesia as seen by the high proportion of responders to deutetrabenazine treatment in the AIM-TD study. *The American Academy of Neurology 2017 Annual Meeting, Boston, MA April 22-28, 2017.* 2017.

10. Anderson KE, Factor SA, Jimenez-Shahed J, et al. Evaluating fixed-dose deutetrabenazine for the treatment of moderate to severe tardive dyskinesia in the AIM-TD study. *The American Psychiatric Association 2017 Annual Meeting, San Diego CA; May 20-24, 2017.* 2017.

11. Fernandez HH, Stamler D, Davis MD, et al. Improvements in clinical global impression of change with deutetrabenazine treatment in tardive dyskinesia from the ARM-TD and AIM-TD studies. *The American Psychiatric Association 2017 Annual Meeting, San Diego CA; May 20-24, 2017.* 2017.

12. Anderson KE, Stamler D, Davis MD, et al. Deutetrabenazine for the treatment of tardive dyskinesia: Results from an open-label, long-term study. *The American Psychiatric Association 2017 Annual Meeting, San Diego CA; May 20-24, 2017.* 2017.

13. Fernandez HH, Factor SA, Hauser RA, et al. Randomized controlled trial of deutetrabenazine for tardive dyskinesia: The ARM-TD study. *Neurology.* 2017;88(21):2003-2010.

14. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature Mortality Among Adults With Schizophrenia in the United States. *JAMA psychiatry.* 2015;72(12):1172-1181.

15. Hayes JF, Miles J, Walters K, King M, Osborn DP. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta psychiatrica Scandinavica.* 2015;131(6):417-425.

16. Lenert LA, Ziegler J, Lee T, Sommi R, Mahmoud R. Differences in health values among patients, family members, and providers for outcomes in schizophrenia. *Medical care.* 2000;38(10):1011-1021.

17. Wang PS, Ganz DA, Benner JS, Glynn RJ, Avorn J. Should clozapine continue to be restricted to third-line status for schizophrenia?: a decision-analytic model. *The journal of mental health policy and economics.* 2004;7(2):77-85.

18. Glennie JL. Pharmacoeconomic evaluations of clozapine in treatmentresistant schizophrenia and risperidone in chronic schizophrenia. *Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment (CCOHTA), July 1997.* 1997.

19. Oh PI, Iskedjian M, Addis A, Lanctot K, Einarson TR. Pharmacoeconomic evaluation of clozapine in treatment-resistant schizophrenia: a cost-utility analysis. *The Canadian journal of clinical pharmacology = Journal canadien de pharmacologie clinique.* 2001;8(4):199-206.

20. Factor SA, Hauser RA, Siegert S, Liang GS, O'Brien CF. KINECT 3: A randomized, double-blind, placebo-controlled phase 3 trial of valbenazine (NBI-98854) for tardive dyskinesia. *Movement Disorders.* 2016;31 suppl 2:S692.

21. Remington G, Comella CL, Grigoriadis D, Liang GS, Burke J, O'Brien CF. Safety and tolerability of valbenazine (NBI-98854) in subjects with tardive dyskinesia: Results of long-term exposure data from three studies. *55th Annual Meeting of the American College of Neuropsychopharmacology, Dec 4-8, 2016; Hollywood, FL.* 2016.

22. Ascher-Svanum H, Zhu B, Faries D, Peng X, Kinon BJ, Tohen M. Tardive dyskinesia and the 3-year course of schizophrenia: results from a large, prospective, naturalistic study. *The Journal of clinical psychiatry.* 2008;69(10):1580-1588.

23. Caroff SN, Davis VG, Miller DD, et al. Treatment outcomes of patients with tardive dyskinesia and chronic schizophrenia. *The Journal of clinical psychiatry.* 2011;72(3):295-303.