MED-MSL-TD-US-0125_v4

Cost-effectiveness Analysis (CEA) of Valbenazine Compared with Deutetrabenazine for the Treatment of Tardive Dyskinesia

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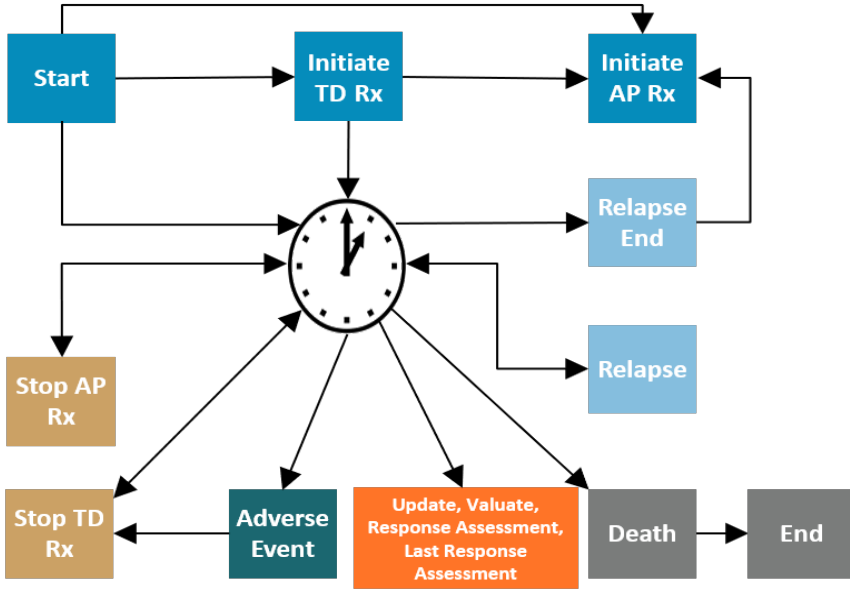
CEA: Study Objective & Model Overview

- Study Objective[1]:
  - Evaluate clinical and economic outcomes associated with valbenazine compared with deutetrabenazine in simulated patients with tardive dyskinesia (TD) using a model that accounted for multiple dimensions of patient health status
  - There are no head-to-head trials of valbenazine and deutetrabenazine, so probabilities of response used in the model were calculated based on an indirect treatment comparison (ITC) of results from individual trials with one drug or the other, using only those metrics reported across trials
- Model Overview[1]:
  - A discretely integrated condition event (DICE) model[2,3] was used to evaluate clinical and economic outcomes associated with valbenazine and deutetrabenazine treatment of TD
  - The model conceptualizes "conditions" that reflect aspects of the model or patient attributes that persist, and "events" that reflect points in time when conditions may change



AP, antipsychotic; Rx, prescription; TD, tardive dyskinesia; Discretely integrated condition event (DICE) Model: Times to events are initially determined at the start of the model. These times are periodically revised during Update, Valuate, Response Assessment, and Last Response Assessment events, which are part of the scheduling process represented by the clock, and when other events occur, as indicated by arrowheads.

1. Ganz ML, et al. J Med Econ. 2021;24(1):103-113. 2. Caro JJ, et al. Pharmacoeconomics. 2016;34(7):665–672.
3. Moller J, et al. Pharmacoeconomics. 2017;35(10):1103–1109.

CEA: Patient Population and Analysis Design

- A synthetic population of 1,000 simulated patients with demographic and clinical characteristics derived from population statistics in the KINECT 3 trial[1] of valbenazine was created and used in the model[2]
- Simulated patients could have only one underlying psychiatric condition: schizophrenia, bipolar disorder, or major depressive disorder (MDD)[2]
- The model was analyzed from a US third-party payer perspective over a 5-year time horizon[2]
    - Only direct costs (drug acquisition costs, disease management costs, and relapse treatment costs) were included in the analysis
- The primary health outcomes assessed were Quality Adjusted Life Years (QALYs), life years, proportion responding to treatment at 1 year, and number of psychiatric relapses[2]

1. Hauser RA, et al. Am J Psychiatry. 2017;174(5):476–484. 2. Ganz ML, et al. J Med Econ. 2021;24(1):103-113.

CEA: Key Assumptions

- All simulated patients began the model simulation with TD and doses of their antipsychotic medications optimized
- During the first 24 weeks of treatment with valbenazine or deutetrabenazine, simulated patients were assessed every 8 weeks for response, defined in the base case as 50% improvement in AIMS total score among simulated patients with any psychiatric condition at baseline (i.e., base case scenario)
  - Simulated patients who responded at a given assessment suffered no disutility due to TD until at least the next assessment
- A final assessment of response was conducted at Week 48, at which time responders continued TD treatment until death, and non-responders discontinued TD treatment
- Simulated patients who discontinued one TD treatment did not attempt another
- All simulated patients with a psychiatric diagnosis were at risk of discontinuing their antipsychotic medications, putting them at increased risk of relapse
- Alternative scenarios: Clinical Global Impression of Change (CGIC) score ≤2 (rating of "much improved" or "very much improved") was used as the definition of response, and 50% improvement in AIMS total score was used as the response criterion among simulated patient subgroups
  - Alternative scenarios utilized the same assumptions

Ganz ML, et al. J Med Econ. 2021;24(1):103-113.

CEA: Clinical Inputs – Dosing & Probability of Response

Average Daily TD Medication Doses[a,b]				
Drug/Dose	**Proportion of Patients**			
Valbenazine 40 mg	0.200			
Valbenazine 80 mg	0.800			
Deutetrabenazine 24 mg	0.270			
Deutetrabenazine 36 mg	0.270			
Deutetrabenazine 48 mg	0.460			
Probability of Response[c]				
	≥50% Improvement in AIMS		**CGIC Score ≤2**	
Week	**Valbenazine**	**Deutetrabenazine**	**Valbenazine**	**Deutetrabenazine**
Week 8	35%	19%	46%	27%
Week 16	40%	23%	59%	38%
Week 24	47%	28%	79%	61%
Week 48	51%	31%	83%	67%
ITC odds ratio (valbenazine vs deutetrabenazine)	2.30		2.34	

[a]Average cohort dose: 72.0 mg/day for valbenazine, 38.3 mg/day for deutetrabenazine.
[b]Calculated from Factor et al 2017, Marder et al 2019, Anderson et al 2017, Fernandez et al 2017, and Fernandez et al 2019.
[c]Calculated from Aggarwal et al 2019; response to treatment defined as ≥50% improvement in AIMS total score (sum of items 1-7) or CGIC score ≤2.
AIMS, Abnormal Involuntary Movement Scale; CGIC, Clinical Global Impression of Change; ITC, indirect treatment comparison; MDD, major depressive disorder; TD, tardive dyskinesia.

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CEA: Clinical Inputs – Antipsychotic Treatment Discontinuation, Psychiatric Condition Relapses & Mortality

Parameters for Antipsychotic Treatment Discontinuation[a]			
Patient Population	**Schizophrenia**	**Bipolar Disorder**	**MDD**
Weibull parameters (γ, λ), Patients with TD	0.783, 0.952	0.914, 1.268	0.914, 1.268
Hazard Ratio, TD Responder	0.593	0.593	0.593
Psychiatric Disorder Annual Risk of Relapse by Antipsychotic Medication Status[b]			
Medication Status	**Schizophrenia**	**Bipolar Disorder**	**MDD**
On Medication	0.315	0.528	0.528
Off Medication	1.022	1.050	1.050
Psychiatric Relapse Sequelae[c]			
Parameter	**Schizophrenia**	**Bipolar Disorder**	**MDD**
Proportion Hospitalized	0.564	0.564	0.564
Duration of Hospitalization, days	10.7	6.9	6.5
Duration of Outpatient Treatment, days	9.0	9.0	9.0
Hazard Ratios for Mortality by Psychiatric Condition[d]			
Gender	**Schizophrenia**	**Bipolar Disorder**	**MDD**
Male	2.210	1.750	0.880
Female	2.660	2.090	2.140

[a]Derived from Greene et al 2018 and Prater et al 2018.
[b]Calculated from Leucht et al 2012, Di Capite et al 2018, and Derry et al 2007.
[c]Derived from Panish et al 2013, Park et al 2014, Rajagopalan et al 2013, and Ascher-Svanum et al 2010.
[d]Calculated from Crump et al 2013 and Chiu et al 2018.
AIMS, Abnormal Involuntary Movement Scale; CGIC, Clinical Global Impression of Change; DTBZ, deutetrabenazine; ITC, indirect treatment comparison; MDD, major depressive disorder; TD, tardive dyskinesia; VBZ, valbenazine.

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CEA: Tardive Dyskinesia Treatment Cost Inputs

Daily Medication Costs		
Drug	**Daily Dose (mg)[a]**	**Daily Cost[b] (2017 US $)**
Valbenazine	40	139.92
Valbenazine	80	151.48
Deutetrabenazine	12	83.94
Deutetrabenazine	18	92.42
Deutetrabenazine	24	125.90
Deutetrabenazine	30	178.35
Deutetrabenazine	36	188.84
Deutetrabenazine	42	220.31
Deutetrabenazine	48	251.79
Antipsychotic[c]	-	17.35

[a]Average cohort dose: 72.0 mg/day for valbenazine, 38.3 mg/day for deutetrabenazine.
[b]Based on 27% discount to the Wholesale Acquisition Cost.
[c]Calculated from Gilmer et al 2004.
TD, tardive dyskinesia.

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CEA: Annual Disease Management Costs & Psychiatric Disorder Relapse Costs

Annual Disease Management Costs[a]		
Disorder	**Cost with TD (2017 US $)**	**Cost without TD (2017 US $)**
Schizophrenia	7,909.94	5,361.92
Bipolar Disorder	3,983.06	1,435.04
Major Depressive Disorder	3,983.06	1,435.04
No Psychiatric Disorder	2,548.02	--
Psychiatric Disorder Relapse Costs[b]		
Disorder	**Hospital Costs (2017 US $)**	**Outpatient Costs (2017 US $)**
Schizophrenia	853.72	84.13
Bipolar Disorder	839.05	84.13
Major Depressive Disorder	546.08	84.13

[a]Calculated from Gilmer et al 2004 and Guo et al 2008.
[b]Calculated from Park et al 2014.
TD, tardive dyskinesia.

Ganz ML, et al. J Med Econ. 2021;24(1):103-113.

CEA: Model Inputs

- The mean utilities for baseline psychiatric conditions of schizophrenia, bipolar disorder, and MDD were 0.83, 0.80, and 0.80, respectively[1]
- A utility decrement of 0.121 was applied to reflect TD[2-4]
- Utility decrements of 0.081, 0.118, and 0.118 were applied to reflect relapses in schizophrenia, bipolar disorder, and MDD, respectively[1]
- Mortality was modeled using estimates from the general population adjusted to reflect condition-specific hazard ratios of the underlying psychiatric disorders[5,6]
- The hazard ratio for mortality used for simulated patients with TD was 1.900[7]
- Costs, quality-adjusted life years (QALYs), and life years were discounted at an annual rate of 3%[8]

MDD, major depressive disorder; TD< tardive dyskinesia.

1. Institute for Clinical and Economic Review. Final evidence report: VMAT2 inhibitors for tardive dyskinesia: effectiveness and value. Boston (MA); 2017. Available from: http://icerorg.wpengine. com/wp-content/uploads/2020/10/NECEPAC_TD_FINAL_REPORT_122217.pdf. 2. Herdman M, et al. *Qual Life Res*. 2011;20(10):1727–1736. 3. Caroff SN, et al. *J Clin Psychopharmacol*. 2020;40(3):259–268. 4. Caroff SN, et al. Poster Presented at APA; 2019 May 18–22. San Francisco, CA. 5. Crump C, et al. *JAMA Psychiatry*. 2013;70(9):931–939. 6. Chiu M, et al. *J Affect Disord*. 2018;234:117–123. 7. Chong SA, et al. *J Clin Psychopharmacol*. 2009;29(1):5–8. 8. Ganz ML, et al. *J Med Econ*. 2021;24(1):103-113.

CEA: Sensitivity Analysis

- Deterministic sensitivity analyses assessed the impact of varying drug acquisition costs, likelihood of response, risk of relapse, treatment discontinuation during and after the first year, the ITC odds ratio, and hazard ratio for TD mortality by ±20%
- Probabilistic sensitivity analyses that drew random values from the distributions of all the model parameters assessed the likelihood of cost-effectiveness of each intervention relative to a range of willingness-to-pay thresholds ranging from $0 to $300,000 per QALY
- Two scenario analyses were conducted to further assess the robustness of the results to underlying assumptions and to obtain results for potentially important cohorts of simulated patients:
  - Stratification by age (<55 and ≥55 years)
  - Assumption of no effect of response on antipsychotic treatment discontinuation

ITC, indirect treatment comparison; TD, tardive dyskinesia; QALY, quality-adjusted life year.

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CEA: 5-Year Health and Cost Outcomes of Tardive Dyskinesia Treatment with Valbenazine and Deutetrabenazine (1/2)

Modeled Scenario	QALYs (discounted)	LYs (discounted)	Responders at Year 1, % (undiscounted)	Relapses, n (undiscounted)	Total Discounted Costs (2017 US $)	Incremental Costs/QALY (discounted)
Response Criterion: ≥50% Improvement in AIMS Score in Patients with Any Psychiatric Disorder at Baseline (Base Case)						
Deutetrabenazine	3.113	4.239	29%	3.006	$191,618	
Valbenazine	3.231	4.266	48%	2.958	$192,794	$9,951
Response Criterion: CGIC Score ≤2 in Patients with Any Psychiatric Disorder at Baseline						
Deutetrabenazine	3.331	4.296	65%	2.926	$283,208	
Valbenazine	3.432	4.323	80%	2.891	$252,311	Dominant
Response Criterion: ≥50% Improvement in AIMS Score in All Patients Regardless of Psychiatric Condition at Baseline						
Deutetrabenazine	3.162	4.274	29%	2.714	$188,291	
Valbenazine	3.280	4.299	48%	2.657	$189,962	$14,109
Response Criterion: ≥50% Improvement in AIMS Score in Patients with Bipolar Disorder at Baseline						
Deutetrabenazine	3.131	4.355	29%	3.553	$185,630	
Valbenazine	3.250	4.378	49%	3.501	$187,510	$15,866
Response Criterion: ≥50% Improvement in AIMS Score in Patients with Major Depressive Disorder at Baseline						
Deutetrabenazine	3.102	4.299	29%	3.437	$183,006	
Valbenazine	3.222	4.325	49%	3.385	$185,124	$17,637
Response Criterion: ≥50% Improvement in AIMS Score in Patients with Schizophrenia at Baseline						
Deutetrabenazine	3.106	4.181	29%	2.770	$195,839	
Valbenazine	3.225	4.208	48%	2.696	$197,446	$13,474

AIMS, Abnormal Involuntary Movement Scale; CGIC, Clinical Global Impression of Change; LY, life year; QALY, quality-adjusted life year.

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CEA: 5-Year Health and Cost Outcomes of Tardive Dyskinesia Treatment with Valbenazine and Deutetrabenazine (2/2)

Modeled Scenario	QALYs (discounted)	LYs (discounted)	Responders at Year 1, % (undiscounted)	Relapses, n (undiscounted)	Total Discounted Costs (2017 US $)	Incremental Costs/QALY (discounted)
Response Criterion: ≥50% Improvement in AIMS Score in Patients Using Antipsychotic Medications at Baseline						
Deutetrabenazine	3.147	4.279	29%	2.951	$193,459	
Valbenazine	3.263	4.300	48%	2.878	$195,385	$16,547
Response Criterion: ≥50% Improvement in AIMS Score in Patients Who Are Employed at Baseline						
Deutetrabenazine	3.217	4.385	29%	3.127	$195,739	
Valbenazine	3.332	4402	49%	3.052	$197,677	$16,897
Response Criterion: ≥50% Improvement in AIMS Score in Patients Without a Psychiatric Condition at Baseline						
Deutetrabenazine	3.521	4.493	30%	0.000	$152,659	
Valbenazine	3.638	4.509	49%	0.000	$154,868	$18,888
Scenario Analysis: Age < 55						
Deutetrabenazine	3.303	4.500	29.9%	3.210	$200,796	
Valbenazine	3.418	4.515	49.5%	3.119	$202,812	$17,474
Scenario Analysis: Age ≥ 55						
Deutetrabenazine	2.941	4.006	28.5%	2.872	$184,057	
Valbenazine	3.059	4.036	47.0%	2.791	$185,544	$12,593
Scenario Analysis: No Effect of Response on Antipsychotic Treatment Discontinuation						
Deutetrabenazine	3.112	4.239	29.0%	3.110	$190,943	
Valbenazine	3.230	4.266	47.9%	3.124	$191,937	$8,436

AIMS, Abnormal Involuntary Movement Scale; CGIC, Clinical Global Impression of Change; LY, life year; QALY, quality-adjusted life year.

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CEA: 5-Year Discounted Costs (2017 US$) of Tardive Dyskinesia Treatment with Valbenazine and Deutetrabenazine (1/2)

Modeled Scenario	TD Medication	AP Medication	Disease Management	Disease Relapse	Total
Response Criterion: ≥50% Improvement in AIMS Score in Patients with Any Psychiatric Disorder at Baseline (Base Case)					
Deutetrabenazine	$137,589	$15,092	$25,841	$13,095	$191,618
Valbenazine	$140,240	$15,839	$23,949	$12,766	$192,794
Response Criterion: CGIC Score ≤2 in Patients with Any Psychiatric Disorder at Baseline					
Deutetrabenazine	$231,644	$16,423	$22,485	$12,655	$283,208
Valbenazine	$201,595	$16,976	$20,979	$12,761	$252,311
Response Criterion: ≥50% Improvement in AIMS Score in All Patients Regardless of Psychiatric Condition at Baseline					
Deutetrabenazine	$138,305	$13,770	$24,137	$12,078	$188,291
Valbenazine	$141,677	$14,419	$22,175	$11,691	$189,962
Response Criterion: ≥50% Improvement in AIMS Score in Patients with Bipolar Disorder at Baseline					
Deutetrabenazine	$140,726	$14,443	$17,817	$12,644	$185,630
Valbenazine	$144,097	$15,133	$15,774	$12,505	$187,510
Response Criterion: ≥50% Improvement in AIMS Score in Patients with Major Depressive Disorder at Baseline					
Deutetrabenazine	$138,657	$14,526	$19,245	$10,579	$183,006
Valbenazine	$142,645	$15,229	$17,257	$9,992	$185,124

AIMS, Abnormal Involuntary Movement Scale; AP, antipsychotic; CGIC, Clinical Global Impression of Change; TD, tardive dyskinesia.

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CEA: 5-Year Discounted Costs (2017 US$) of Tardive Dyskinesia Treatment with Valbenazine and Deutetrabenazine (2/2)

Modeled Scenario	TD Medication	AP Medication	Disease Management	Disease Relapse	Total
Response Criterion: ≥50% Improvement in AIMS Score in Patients with Schizophrenia at Baseline					
Deutetrabenazine	$136,316	$15,579	$29,974	$13,969	$195,839
Valbenazine	$139,837	$16,342	$28,098	$13,168	$197,446
Response Criterion: ≥50% Improvement in AIMS Score in Patients Using Antipsychotic Medications at Baseline					
Deutetrabenazine	$137,170	$16,043	$27,101	$13,146	$193,459
Valbenazine	$140,949	$16,782	$25,134	$12,520	$195,385
Response Criterion: ≥50% Improvement in AIMS Score in Patients Who Are Employed at Baseline					
Deutetrabenazine	$139,801	$15,703	$26,591	$13,644	$195,739
Valbenazine	$143,568	$16,378	$24,561	$13,170	$197,677
Response Criterion: ≥50% Improvement in AIMS Score in Patients Without a Psychiatric Condition at Baseline					
Deutetrabenazine	$144,486	--	$8,173	--	$152,659
Valbenazine	$148,863	--	$6,005	--	$154,868

AIMS, Abnormal Involuntary Movement Scale; AP, antipsychotic; CGIC, Clinical Global Impression of Change; TD, tardive dyskinesia.

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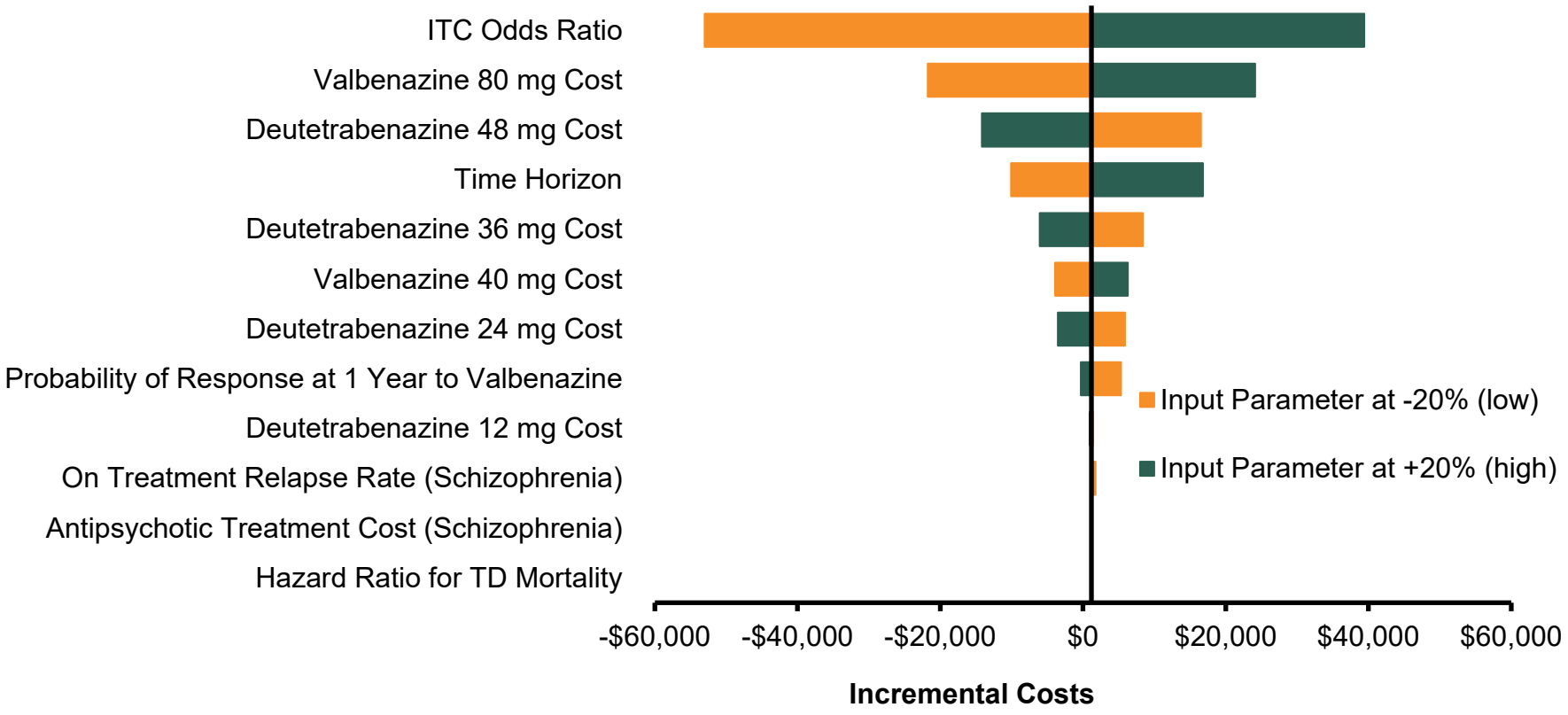
CEA: Tornado Plots for Deterministic Sensitivity Analysis of Valbenazine Compared with Deutetrabenazine

Incremental Costs



ITC, indirect treatment comparison; TD, tardive dyskinesia.

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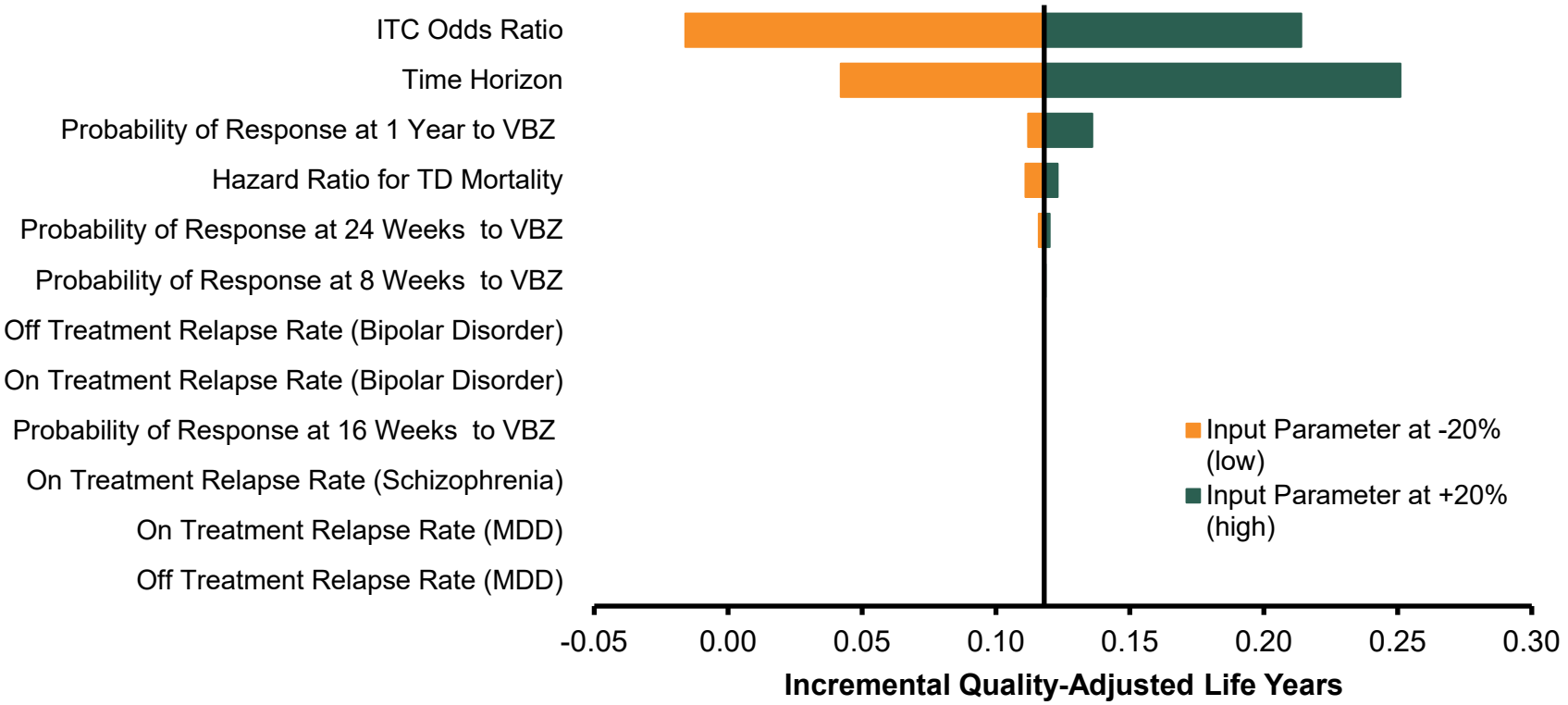
CEA: Tornado Plots for Deterministic Sensitivity Analysis of Valbenazine Compared with Deutetrabenazine

Incremental QALYs



ITC, indirect treatment comparison; MDD, major depressive disorder; QALY, quality-adjusted life year; TD, tardive dyskinesia; VBZ, valbenazine.

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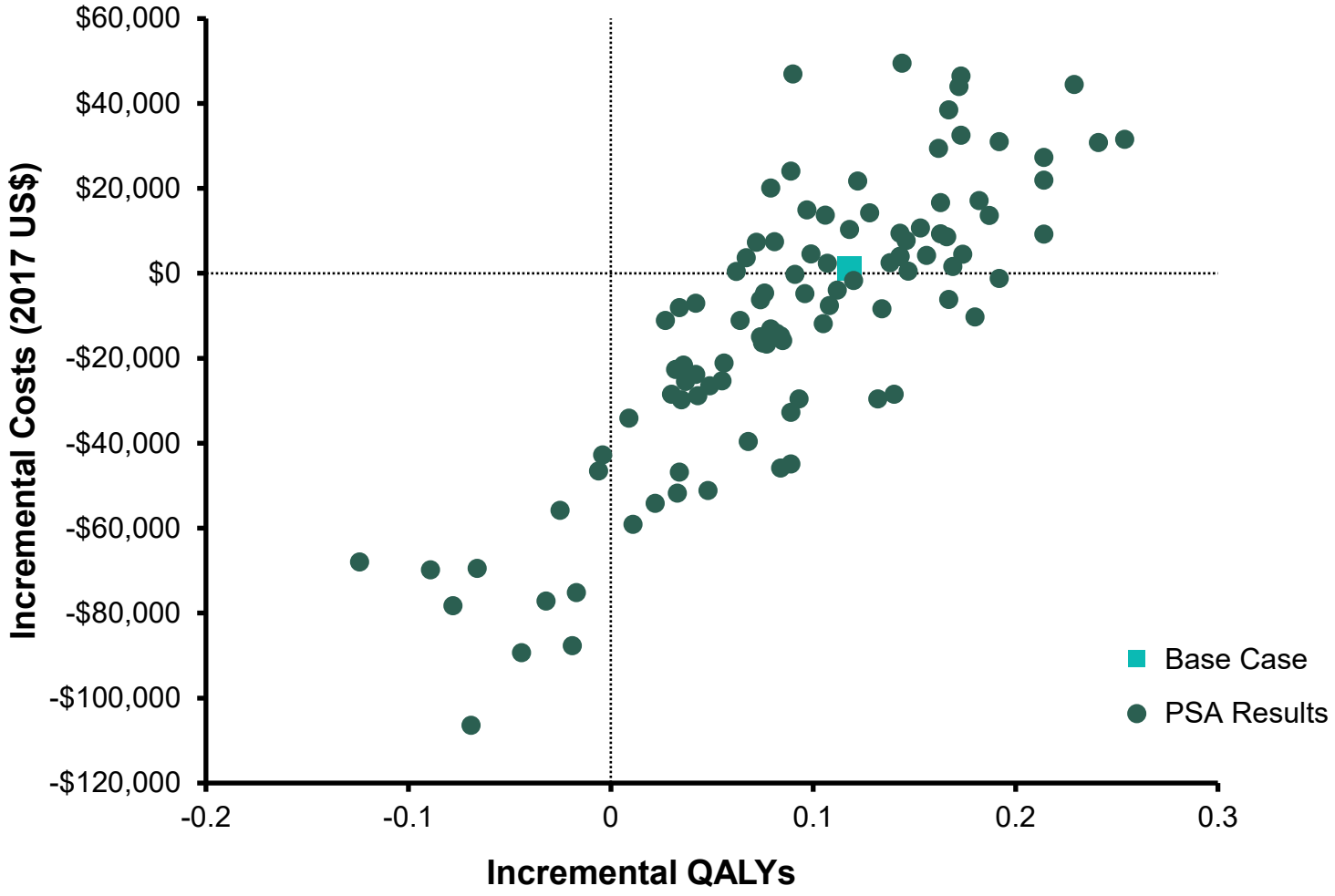
CEA: Cost-Effectiveness Plane for Probabilistic Sensitivity Analysis of Valbenazine Compared with Deutetrabenazine



Analysis based on 100 model simulations using response criterion of ≥50% improvement in AIMS total score in simulated patients with any psychiatric diagnosis at baseline.
AIMS, Abnormal Involuntary Movement Scale; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

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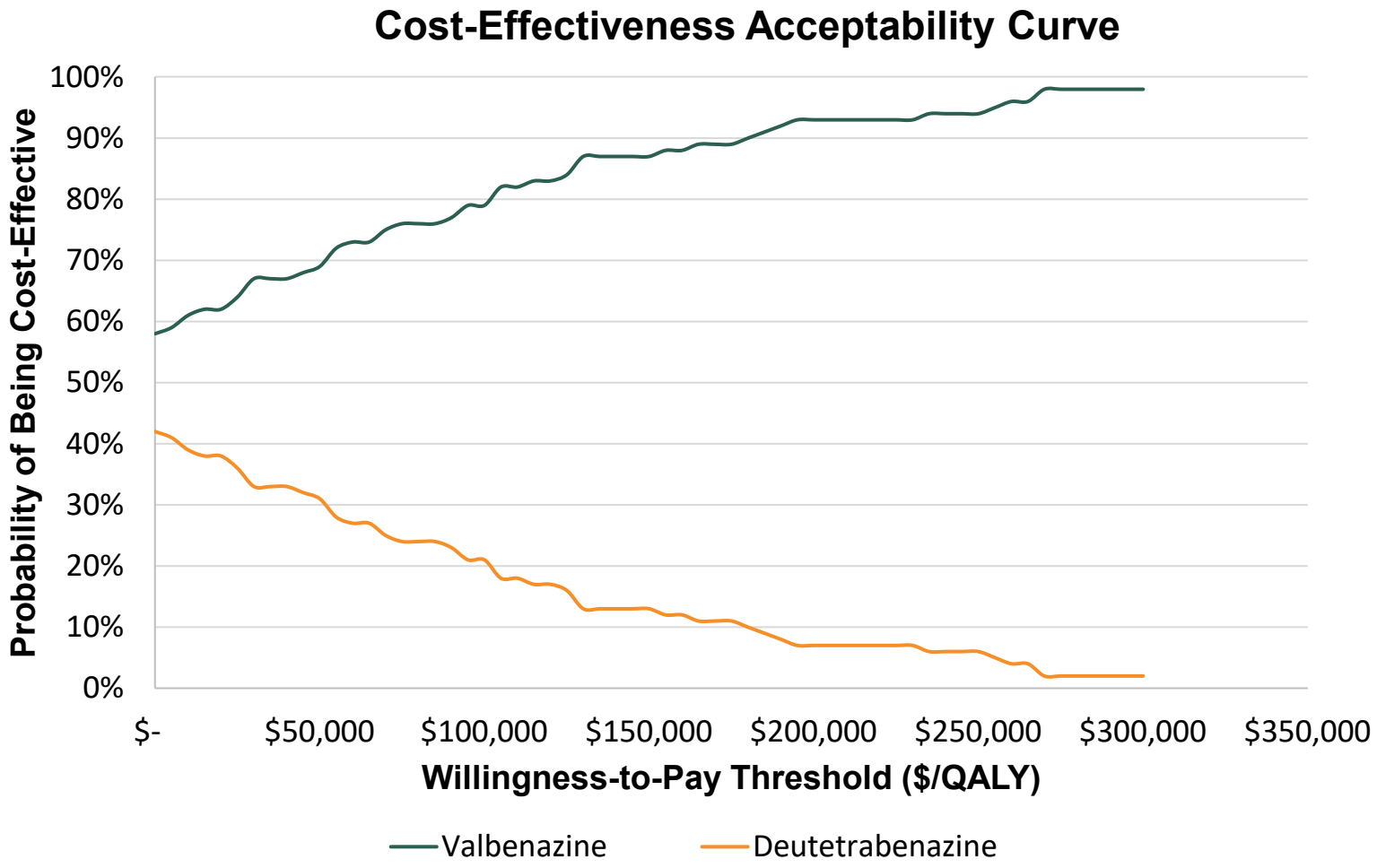
CEA: Cost-Effectiveness Acceptability Curves for Valbenazine and Deutetrabenazine



QALY, quality-adjusted life year.

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CEA: Base Case Analysis[a] Results

- Simulated patients treated with valbenazine experienced reduced TD severity, lived longer, and accrued more QALYs compared with simulated patients who received deutetrabenazine
- Valbenazine was associated with lower total costs (i.e., “dominated” deutetrabenazine) in the analysis of simulated patients with any psychiatric disorder at baseline when response was measured by CGIC score ≤ 2
- In all other scenarios, the ICERs for valbenazine ranged from $9,951 (base case) to $18,888 (analysis of simulated patients without a psychiatric condition at baseline)
- Probability of response to valbenazine and deutetrabenazine at 1 year was approximately 50% greater for the CGIC measure compared with the AIMS criterion
- Drug acquisition costs were the largest contributor to total costs and were higher for valbenazine in all scenarios (except when response was measured using CGIC score)

[a]Base Case Analysis: 50% improvement from baseline in AIMS total score among simulated patients with any underlying psychiatric condition at baseline
TD, tardive dyskinesia; QALY, quality-adjusted life year; CGIC, Clinical Global Impression of Change; ICER, Incremental cost-effectiveness ratios (defined as the differences in discounted QALYs between VBZ and DTBZ divided by the differences in discounted costs between those treatments); AIMS, Abnormal Involuntary Movement Scale; WTP, willingness-to-pay.

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CEA: Sensitivity Analyses Results

- The results were most sensitive to the ITC odds ratio[a], the acquisition cost of valbenazine 80mg[b], and acquisition cost of deutetrabenazine 48mg[c]
- In almost all cases, valbenazine remained cost effective compared with deutetrabenazine when varying model inputs by ±20%
- In all analyses, incremental lifetime costs of valbenazine treatment compared with deutetrabenazine remained below a threshold of $50,000
- Compared with valbenazine, deutetrabenazine is generally not a cost-effective option at any WTP threshold ≤ $300,000 per QALY

[a]incremental lifetime costs for VBZ compared with DTBZ ranging from $53,022 to $39,410. [b]incremental lifetime costs compared with DTBZ ranging from $21,771 to $24,123. [c]incremental lifetime costs compared with deutetrabenazine ranging from $14,167 to $16,519.
TD, tardive dyskinesia; QALY, quality-adjusted life year; CGIC, Clinical Global Impression of Change; ICER, Incremental cost-effectiveness ratios (defined as the differences in discounted QALYs between VBZ and DTBZ divided by the differences in discounted costs between those treatments); AIMS, Abnormal Involuntary Movement Scale; WTP, willingness-to-pay.

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CEA: Summary

- In simulated patients with TD, treatment with valbenazine was associated with longer life expectancy and better quality-of-life, measured by QALYs, compared with deutetrabenazine
- Measures of global improvement may be more sensitive to improvements in quality of life than improvement in AIMS score
- Over a lifetime horizon, valbenazine was more effective than deutetrabenazine, and either less costly or associated with increased costs well below established cost per QALY thresholds, depending on the response criterion evaluated
  - In the base case analysis[a] simulated patients who were treated with valbenazine experienced reduced TD severity, lived longer, and accrued more QALYs compared with simulated patients who received deutetrabenazine
  - Regardless of the response criterion or subgroup analyzed, a larger proportion of simulated patients receiving valbenazine responded to treatment at 1 year than simulated patients receiving deutetrabenazine, resulting in an increased likelihood of continuing treatment, increased life expectancy, fewer psychiatric relapses, and increased accumulation of QALYs
  - Valbenazine was associated with lower total costs (i.e., “dominated” deutetrabenazine) in the analysis of simulated patients with any psychiatric disorder at baseline when response was measured by CGIC score ≤ 2

[a]Base Case Analysis: 50% improvement from baseline in AIMS total score among simulated patients with any underlying psychiatric condition at baseline.
TD, tardive dyskinesia; QALY, quality-adjusted life year; CGIC, Clinical Global Impression of Change; AIMS, Abnormal Involuntary Movement Scale.

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