Product Overview: Valbenazine & Deutetrabenazine in Tardive Dyskinesia

NEUROCRINE® BIOSCIENCES

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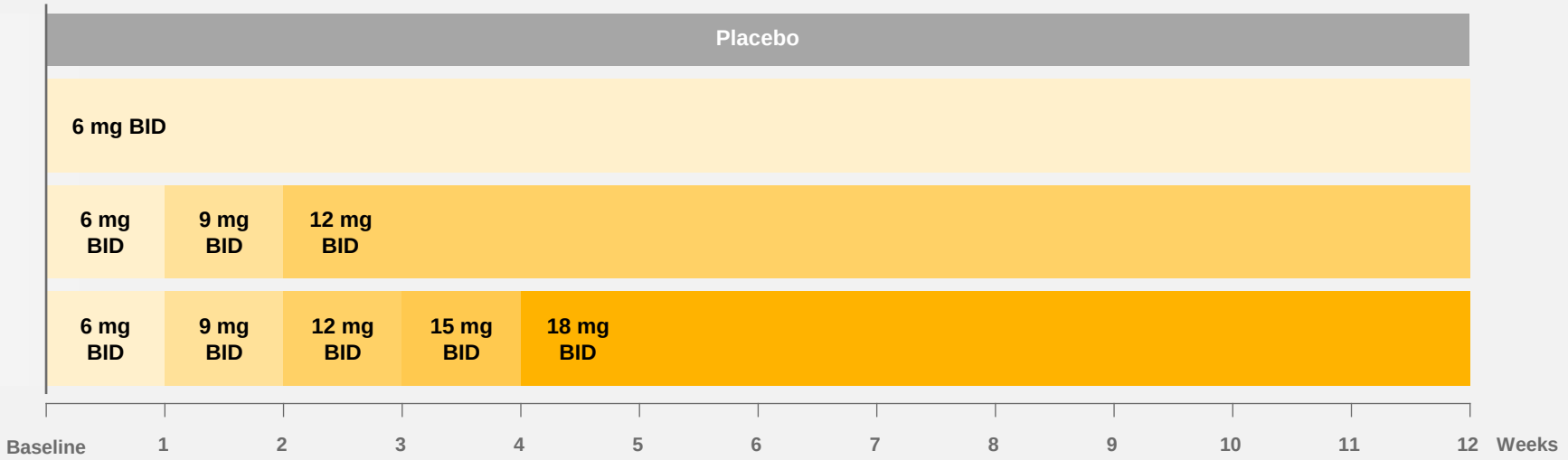
KINECT® 3 & AIM-TD

These slides are not meant to imply direct comparisons and should not be used to suggest any direct safety or efficacy comparison

KINECT 3 & AIM-TD: Study Design

KINECT 3[1]
NTC02274558
Valbenazine

AIM-TD[2]
NTC02291861
Deutetrabenazine



VBZ, valbenazine; dTBZ, deutetrabenazine; BID, twice a day.
[a]80 mg group started on 40 mg for 1 week.
1. Hauser RA et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Anderson KE et al. *Lancet Psychiatry*. 2017;4(8):595-604.

KINECT 3 & AIM-TD: Key Inclusion/Exclusion Criteria

KINECT 3[1]

Key inclusion criteria:

- *Diagnostic and Statistical Manual of Mental Disorders* (e.g., DSM-IV) diagnosis of schizophrenia, schizoaffective disorder, or mood disorder
  - Required to be psychiatrically stable prior to study entry[a]
- DSM diagnosis of DRBA-induced TD for ≥3 months prior to screening
- Moderate or severe TD as qualitatively assessed by blinded external reviewers

Key exclusion criteria:

- Active, clinically significant, and unstable medical condition within 1 month prior to screening
- Comorbid movement disorder that was more prominent than TD
- Significant risk for active suicidal ideation, suicidal behavior, or violent behavior

Concomitant medications to treat psychiatric disorders were allowed; stable doses were encouraged

AIM-TD[2]

Key inclusion criteria:

- Diagnosis of DRBA-induced TD for ≥3 months (or 1 month in participants ≥60 years old)
- AIMS score of ≥6 at screening and baseline

Key exclusion criteria:

- Concomitant anticholinergic medications
- Serious untreated or under-treated psychiatric illness
- Comorbid movement disorder other than TD that could interfere with dyskinesia assessment
- Suicidal ideation or suicidal behavior within 6 months of screening
- Hospital Anxiety and Depression Scale (HADS) of ≥11 at screening or baseline
- Fridericia-corrected QT interval >450 msec in men and >460 msec in women

[a] E.g., Brief Psychiatric Rating Scale score <50 at screening.

1. Hauser RA et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Anderson KE et al. *Lancet Psychiatry*. 2017;4(8):595-604.

KINECT 3 & AIM-TD: Baseline Characteristics

	KINECT 3[1]			AIM-TD[2]			
	PBO n=76	VBZ 40 mg n=72	VBZ 80 mg n=79	PBO n=72	dTBZ 6 mg BID n=74	dTBZ 12 mg BID n=73	dTBZ 18 mg BID n=74
Age (yr), mean	57.0	55.3	56.0	54.6	57.0	55.6	58.3
Male (%)	55.3	58.3	49.4	49	43	44	43
AIMS score (items 1-7), mean	9.9	9.7	10.4	9.5	9.6	9.4	10.1
Schizophrenia/ schizoaffective disorder (%)	65.8	66.7	65.8	58	54	68	59
Mood disorder (%)	34.2	33.3	34.2	39	43	25	38

PBO = placebo, VBZ = valbenazine, dTBZ = deutetrabenazine, BID = twice a day, AIMS = abnormal involuntary movement scale.

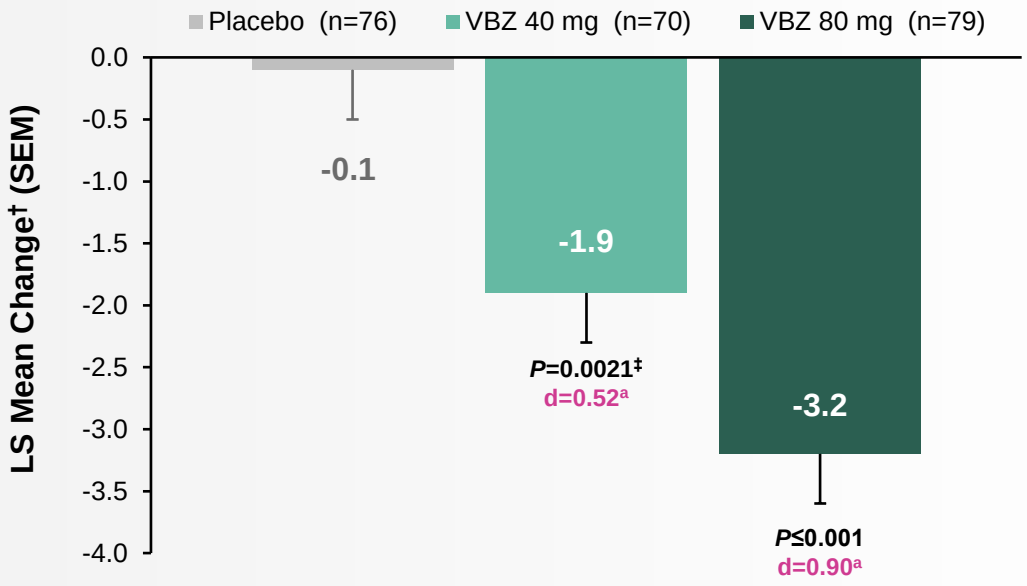
1. Hauser RA et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Anderson KE et al. *Lancet Psychiatry*. 2017;4(8):595-604.

KINECT 3 & AIM-TD: Efficacy Results

KINECT 3[1]*

AIMS CFB at **Week 6**

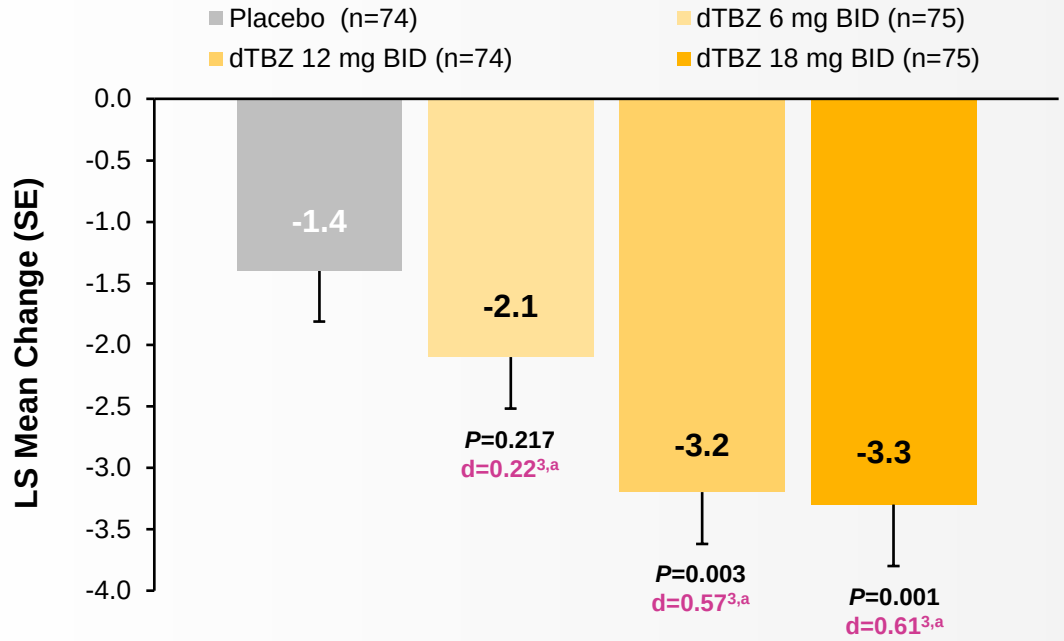
Primary Efficacy Endpoint



AIM-TD[2, ¥]

AIMS CFB at **Week 12**

Primary Efficacy Endpoint



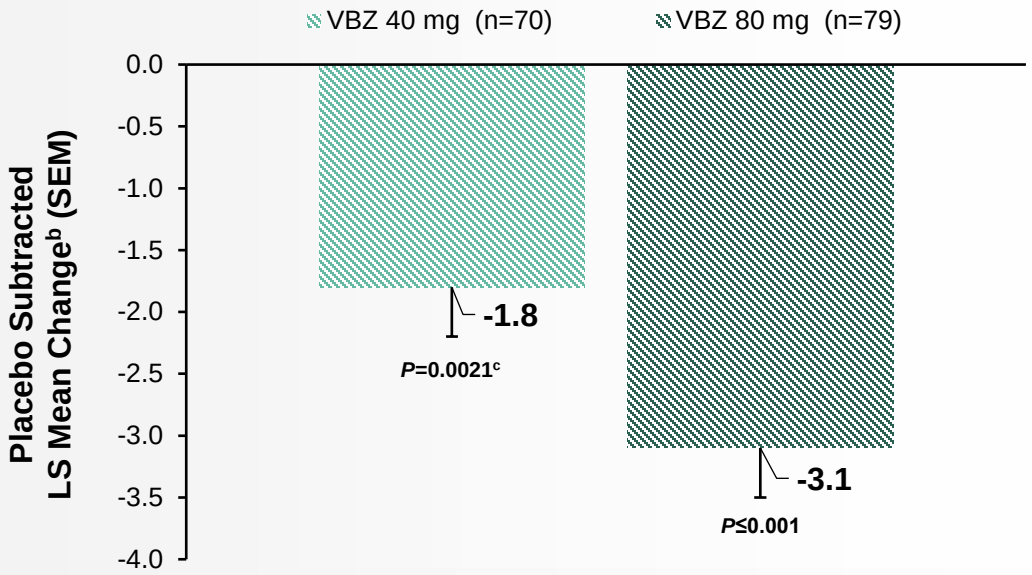
* ITT: Included all randomized participants who had ≥1 post-randomization AIMS value.
¥Modified ITT: included all randomized participants who had a baseline AIMS score of ≥6 with ≥1 post-baseline AIMS assessment.
† LS mean based on the MMRM model, which includes baseline AIMS dyskinesia total score value as a covariate, and treatment group, disease category, visit, treatment group by visit, and baseline by visit interaction as fixed effects, and participant as a random effect.
‡ Nominal p-value, statistical analysis plan-specified hierarchical analysis precluded testing 40mg result for significance.
[a]Cohen's d (treatment effect size).
CFB, change from baseline; NNT, number needed to treat; VBZ, valbenazine; dTBZ, deutetrabenazine; BID, twice a day; ITT, intent-to-treat; LS, least squares.

1. Hauser RA et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Anderson KE et al. *Lancet Psychiatry*. 2017;4(8):595-604. 3. Citrome L. *Int J Clin Pract*. 2017;71(11).

KINECT 3 & AIM-TD: Placebo-Adjusted Efficacy Results

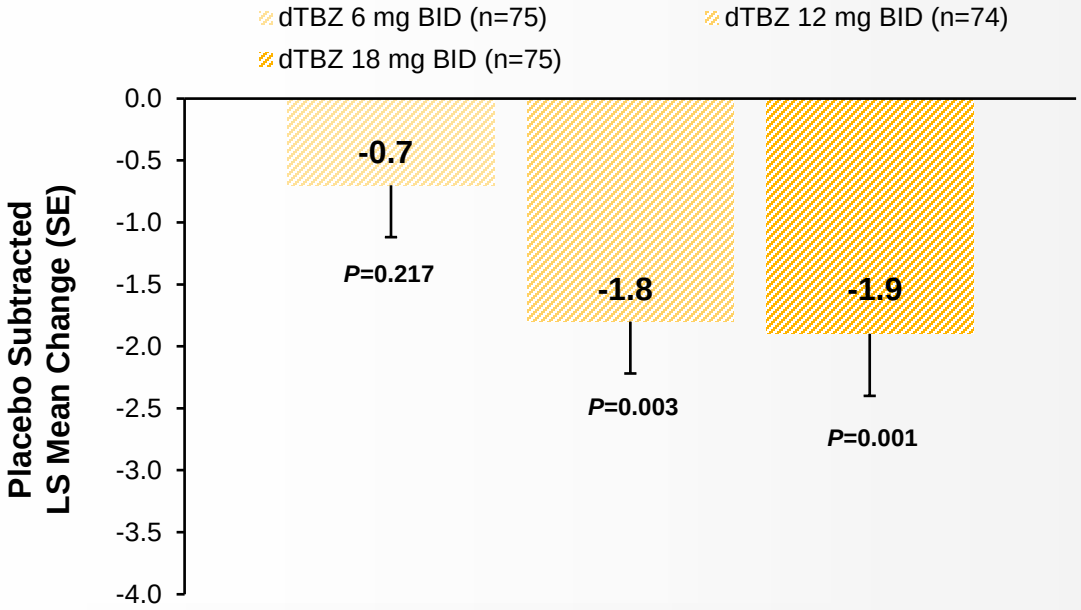
KINECT 3[1,a]

AIMS CFB at **Week 6**
Primary Efficacy Endpoint



AIM-TD[2,d]

AIMS CFB at **Week 12**
Primary Efficacy Endpoint



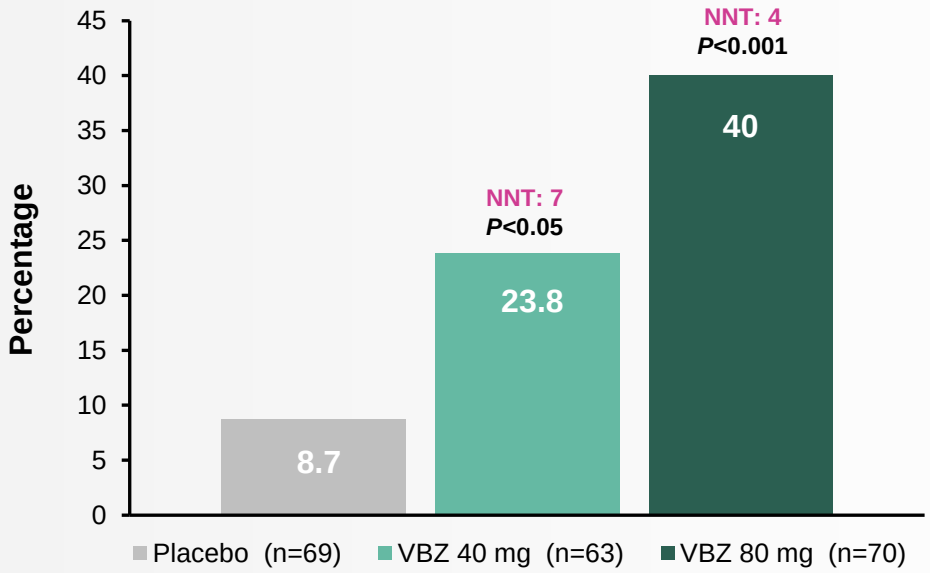
[a]ITT: Included all randomized subjects who had at least one post-randomization AIMS value.
[b]LS mean based on the MMRM model, which includes baseline AIMS dyskinesia total score value as a covariate, and treatment group, disease category, visit, treatment group by visit, and baseline by visit interaction as fixed effects, and subject as a random effect.
[c]Nominal *P*-value, statistical analysis plan-specified hierarchical analysis precluded testing 40 mg result for significance.
[d]Modified ITT: included all randomized subjects who had a baseline AIMS score of 6 or more with at least one post-baseline AIMS assessment.
CI, confidence interval, PBO, placebo, VBZ, valbenazine, dTBZ, deutetrabenazine, BID, twice a day.

1. Hauser RA et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Anderson KE et al. *Lancet Psychiatry*. 2017;4(8):595-604.

KINECT 3 & AIM-TD: ≥50% AIMS Improvement from Baseline

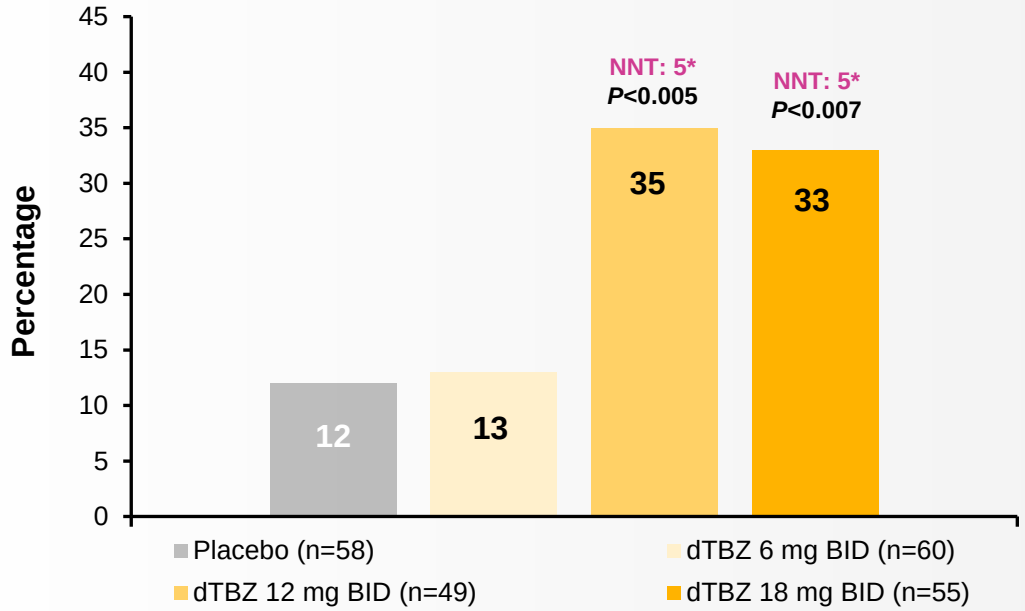
KINECT 3[1]

Percentage of participants who had ≥50% improvement in AIMS score at **Week 6**



AIM-TD[2,3]

Percentage of participants who had ≥50% improvement in AIMS score at **Week 12**



*Using data from AIM-TD, Citrome et al.[3] calculated the NNT based on AIMS responders (defined by a ≥50% reduction from baseline in AIMS dyskinesia score [sum of items 1-7]) at Week 12.
VBZ, valbenazine; dTBZ, deutetrabenazine; BID, twice a day; NNT, number needed to treat.

1. Hauser RA et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Anderson KE et al. *Lancet Psychiatry*. 2017;4(8):595-604. 3. Citrome L. *Int J Clin Pract*. 2017 Nov;71(11).

KINECT 3 & AIM-TD: Safety Results

	KINECT 3[1]			AIM-TD[2]			
	PBO n=76	VBZ 40 n=72	VBZ 80 n=79	PBO n=72	DTBZ 6 mg BID n=74	DTBZ 12 mg BID n=73	DTBZ 36 mg BID n=74
Any TEAE, n	33	29	40	34	36	32	38
Serious TEAE, n	3	4	6	4	2	6	4
Treatment-related AEs, n				19	13	11	18
Discontinuation/withdrawal due to AE, n	4	4	5	2	4	2	3
TEAE leading to dose reduction, n				0	0	1	3
TEAE leading to dose suspension, n				2	3	1	1
Deaths, n	0	0	1*	0	0	1†	1†

*One death, possibly due to cardiovascular event, in 73-year-old African American man; judged by the investigator as unlikely related to study drug.
†Deaths not considered drug related.
AE, adverse event; [Blank], not reported/measured; PBO, placebo; TEAE, treatment-emergent adverse event.
1. Hauser RA. et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Anderson KE et al. *Lancet Psychiatry*. 2017;4(8):595-604.

KINECT 3 & AIM-TD: Safety Results (cont'd)

Adverse events (n)	KINECT 3[1]*			AIM-TD[2]			
	PBO n=76	VBZ 40mg n=72	VBZ 80 mg n=79	PBO n=72	dTBZ 6 mg BID n=74	dTBZ 12 mg BID n=73	dTBZ 36 mg BID n=74
Somnolence	3	4	4	3	0	1	3
Dyskinesia	0	0	3	0	0	1	1
Dry Mouth	1	5	0	0	3	0	2
Arthralgia	1	1	3				
Akathisia	1	3	2	0	0	1	0
Vomiting	0	0	3				
Diarrhea				2	1	3	5
Urinary tract infection	3	3	0				
Anxiety	0	1	2	2	3	2	3
Depression				0	1	3	1
Fatigue	1	2	1	1	1	2	3
Headache	2	2	2	4	5	2	5
Hypertension				1	0	0	3
Muscle Spasms				0	0	0	3
Nausea				7	1	1	1
Nasopharyngitis				1	4	3	2

*Reported in ≥2% of participants in the VBZ group.
[Blank], not reported/measured; PBO, placebo; VBZ, valbenazine; dTBZ, deutetrabenazine; AE, adverse event.
1. Hauser RA et al. *Am J Psychiatry*. 2017;174(5):476-484. 2. Anderson KE et al. *Lancet Psychiatry*. 2017;4(8):595-604.

Valbenazine 60 mg Data

MIDD Modeling & Simulation for Valbenazine 60 mg: Methodology

MIDD DEFINITION

E-R Model

Exposure

Population PK data from:

- Phase 1 studies in healthy adults
- Phase 1b and Phase 2 studies
- Total: 381 participants

+

Response

Data from KINECT 3 DBPC Phase
(6 weeks)

- 40 mg and 80 mg
- Total: 235 participants with TD

=

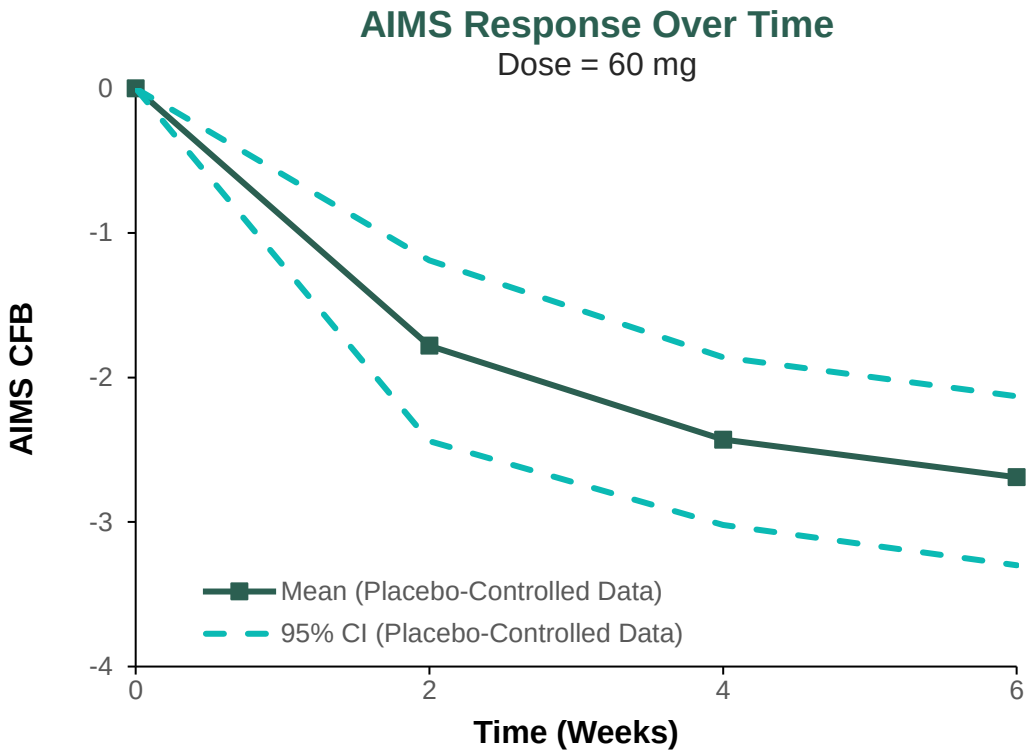
Prediction of 60 mg efficacy through simulation of 1000 clinical trials

Simulated clinical trials included:

- 2,000 virtual participants
- Participants randomized (1:1:1:1) to PBO, 40 mg, 60 mg, and 80 mg

MIDD, model-informed drug development; PK, pharmacokinetic; DBPC, double-blind placebo-control; TD, tardive dyskinesia; PBO, placebo.
Data on File. Neurocrine Biosciences, Inc.

MIDD Modeling & Simulation for Valbenazine 60 mg: AIMS Results



Predicted population mean CFB in AIMS at **Week 6** for **valbenazine 60 mg** is

-2.69

(95% CI: -3.30 to -2.13)

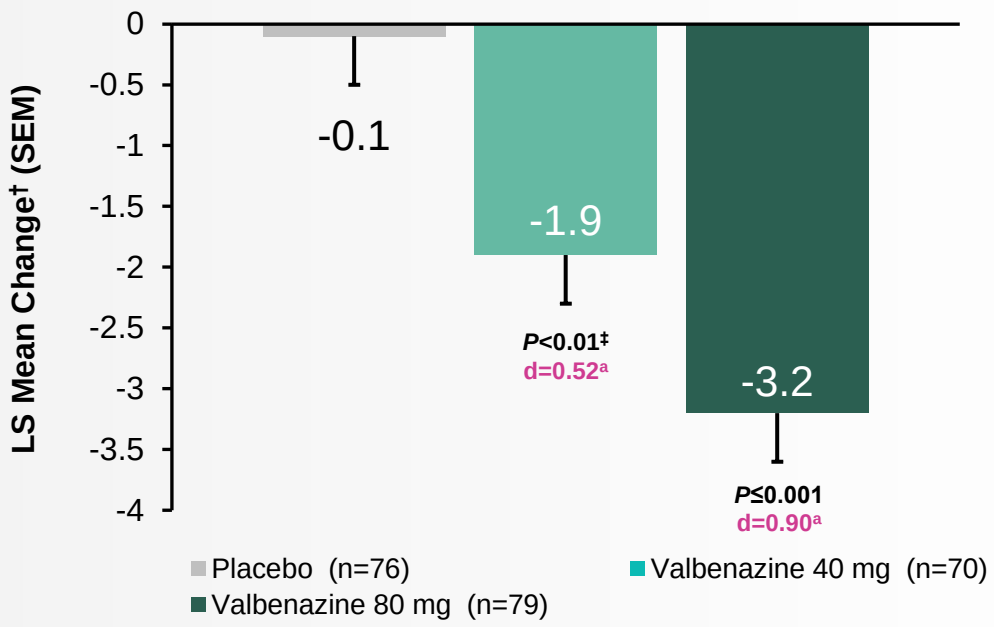
The simulated data set was designed to replicate the KINECT 3 study methodology, dose regimen, and covariate distributions

CFB, change from baseline; MIDD, model-informed drug development; AIMS, Abnormal Involuntary Movement Scale.

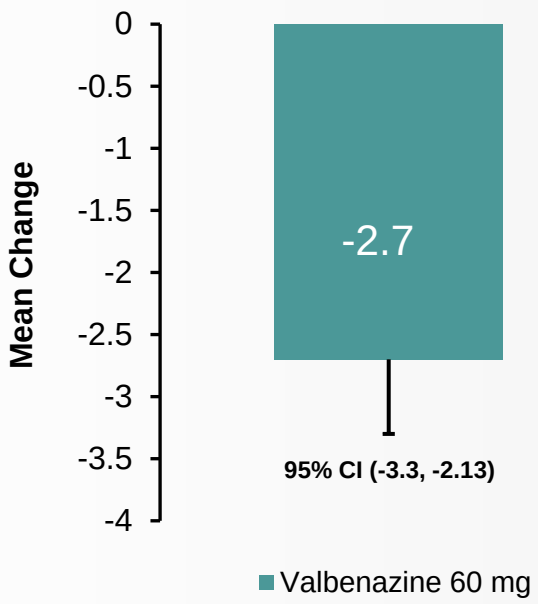
INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

KINECT 3 & MIDD Modeling & Simulation: AIMS Results

AIMS CFB at Week 6
(Efficacy Endpoint of KINECT 3 – ITT Population*)[1]



AIMS CFB at Week 6
(Based on Modeling & Simulation)[2]



ITT: Included all randomized participants who had ≥1 post-randomization AIMS value.
† LS mean based on the MMRM model, which includes baseline AIMS dyskinesia total score value as a covariate, and treatment group, disease category, visit, treatment group by visit, and baseline by visit interaction as fixed effects, and participant as a random effect.
‡ Nominal p-value, statistical analysis plan-specified hierarchical analysis precluded testing 40mg result for significance.
[a]Cohen's d (treatment effect size).
MIDD, model-informed drug development; AIMS, Abnormal Involuntary Movement Scale; CI, confidence interval; ITT, intent-to-treat; LS, least squares.
1. Hauser RA et al. *Am J Psych.* 2017. doi:10.1176/appi.ajp.2017.16091037. 2. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

Long-Term Valbenazine & Deutetrabenazine Clinical Trials: KINECT® 3 Extension & KINECT® 4

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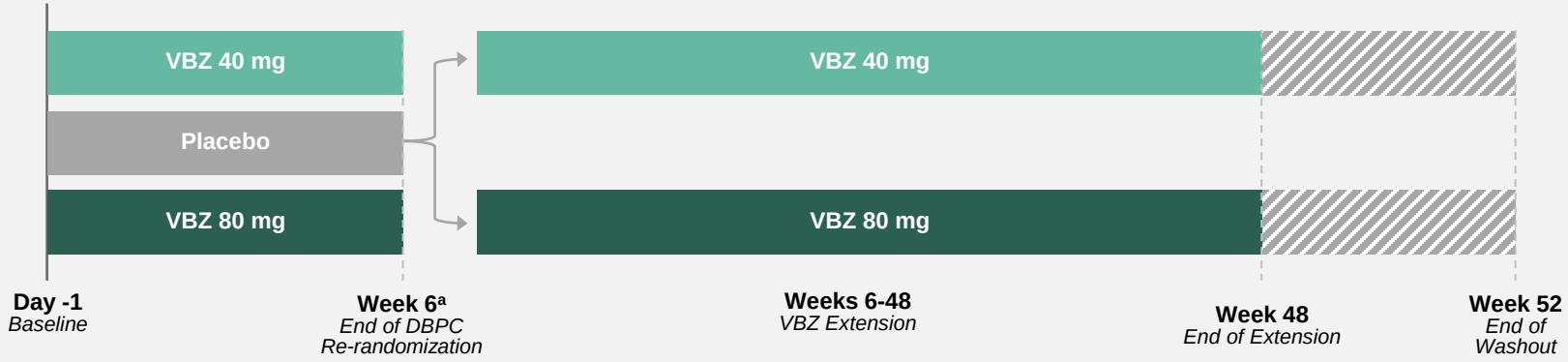
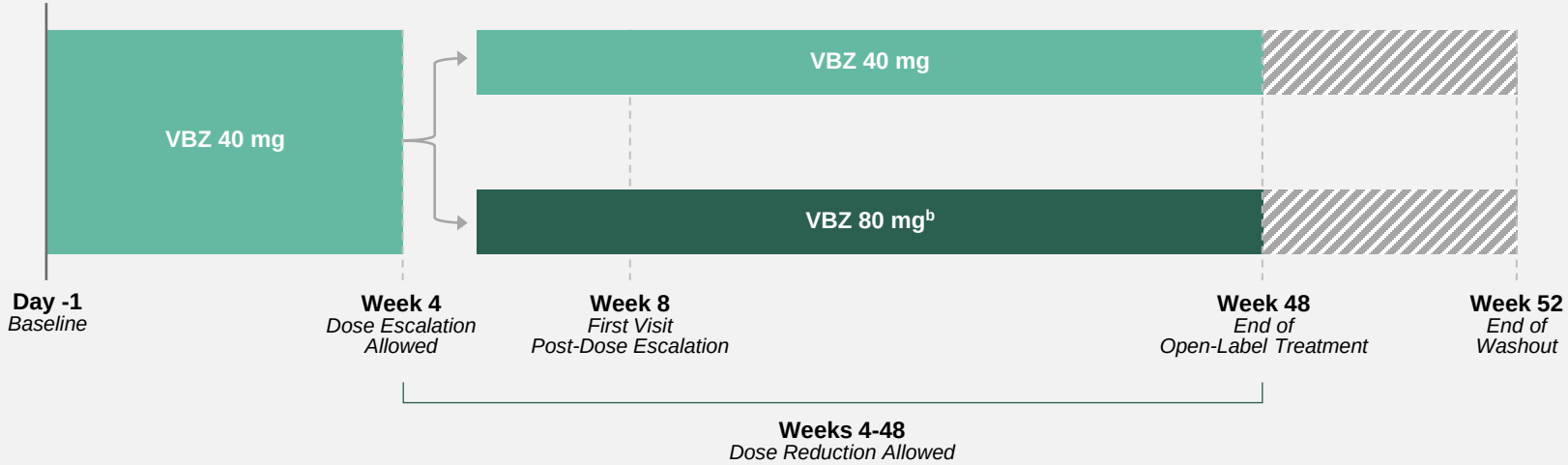
KINECT 3 Extension & KINECT 4: Study Design

KINECT 3 EXTENSION[1]
NTC02274558
Valbenazine



KINECT 4[2]
NCT02405091
Valbenazine



[a]Participants randomized or re-randomized to VBZ 80 mg group started on 40 mg for one week.
[b]Includes participants who had a dose reduction to 40 mg/day due to tolerability issues.
VBZ, valbenazine; DBPC, double-blind placebo-controlled.

1. Factor SA, et al. *J Clin Psychiatry.* 2017;78(9):1344-1350. 2. Marder SR, et al. *J Clin Psychopharmacol*. 2019;39(6):620-627.

KINECT 3 Extension & KINECT 4: Baseline Characteristics

	KINECT 3 Extension[1]		KINECT 4[2,3]	
	Valbenazine 40 mg (n=94)	Valbenazine 80 mg (n=97)	Valbenazine 40 mg (n=45)	Valbenazine 80 mg (n=107)
Age, mean years (SD)	55.8 (9.5)	56 (9.9)	56.8 (11.2)	57.8 (9.0)
Male, n (%)	55 (58.5)	48 (49.5)	21 (46.7)	59 (55.1)
White, n (%)	51 (54.3)	59 (60.8)	26 (57.8)	74 (69.2)
Schizophrenia/schizoaffective disorder, n (%)	61 (64.9)	62 (63.9)	37 (82.2)	76 (71.0)
Mood disorder, n (%)	33 (35.1)	35 (36.1)	8 (17.8)	31 (29.0)
BPRS score, mean (SD)	29.6 (7.5)	28.8 (6.1)	29.2 (6.8)	27.3 (6.6)
AIMS score by central video raters, mean (SD)	9.6 (4)	10.4 (4)	10.2 (3.9)	10.0 (3.9)
AIMS score by site investigator raters, mean (SD)			14.2 (5.5)	15 (4.5)
Receiving concomitant antipsychotic medication, n %	81 (86.2)	80 (82.5)		

[Blank], not reported/measured; PBO, placebo; BPRS, Brief Psychiatric Rating Scale; AIMS, abnormal involuntary movement scale.

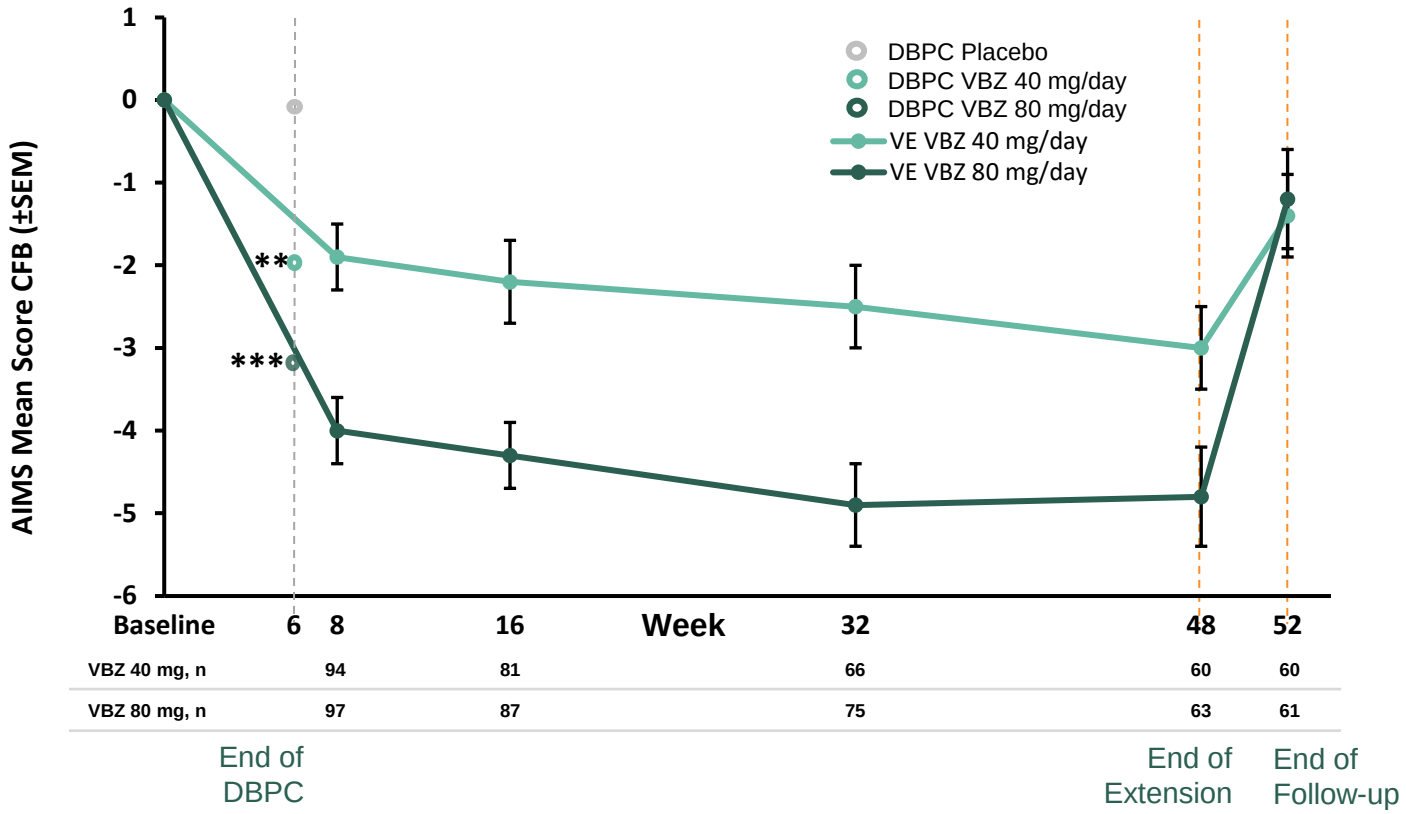
1. Factor SA, et al. *J Clin Psych*. 2017; Nov/Dec;78(9):1344-1350. 2. Marder SR, et al. *J Clin Psychopharmacol*. 2019;39(6):620-627. 3. Marder SR, et al. ACNP 2017; Atlanta, GA.

KINECT 3 Extension & KINECT 4: Effectiveness Data

	KINECT 3 Extension[1]		KINECT 4[2,3]	
	Valbenazine 40 mg (n=60)	Valbenazine 80 mg (n=63)	Vabenazine 40 mg (n=45)	Valbenazine 80 mg (n=107)
AIMS CFB to Week 48, mean	-3.0*	-4.8*	-10.2¥	-11.0¥
AIMS CFB to Week 52, mean	-1.4*	-1.2*	-3.8¥	-4.6¥
CGI-TD Score at Week 48, mean	2.4	2.1	1.7	1.6
CGI-TD Score at Week 52, mean	3.1	3.5	3.6	2.9

*Central video raters, ¥Site investigator rater.
CFB, change from baseline; PBO, placebo; AIMS, abnormal involuntary movement scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia.
1. Factor SA, et al. *J Clin Psych*. 2017; Nov/Dec;78(9):1344-1350. 2. Marder SR, et al. *J Clin Psychopharmacol*. 2019;39(6):620-627. 3. Marder SR, et al. ACNP 2017; Atlanta, GA.

KINECT 3 Extension: AIMS Mean Score Change from Baseline

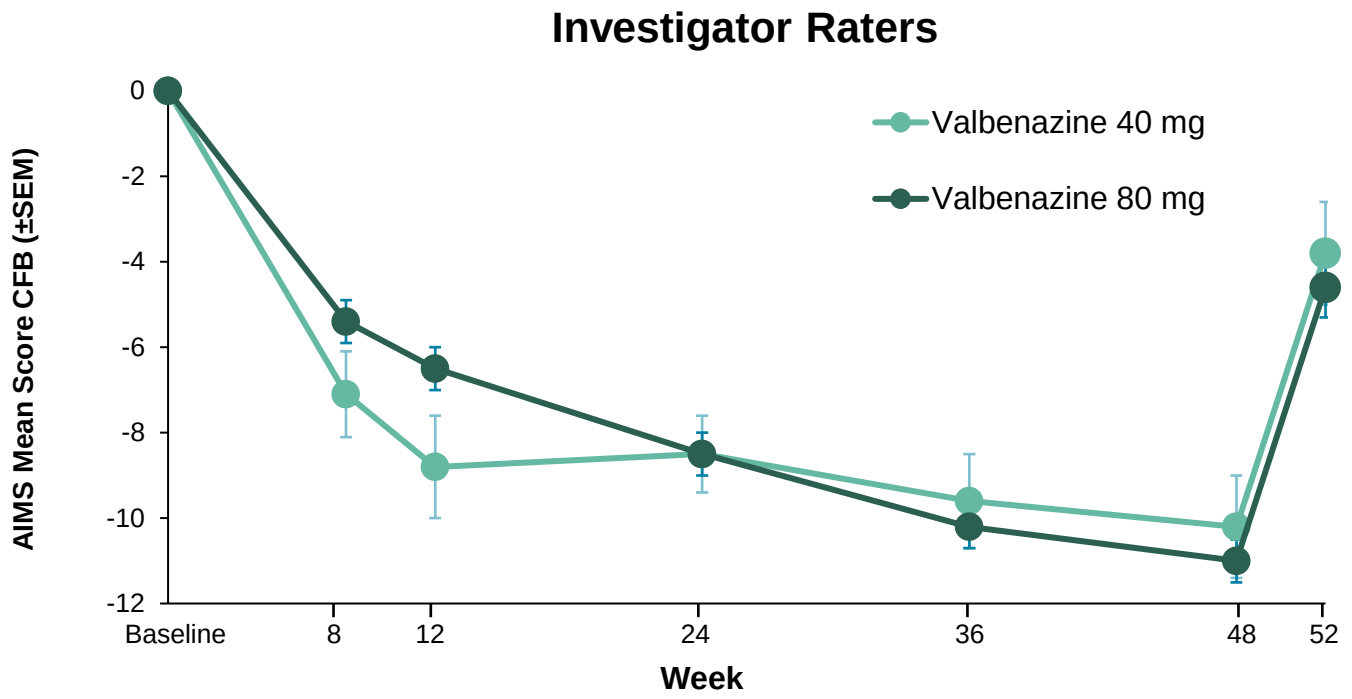


Data for 40 mg and 80 mg combined for extension phase with placebo participants after being re-randomized to 40 mg and 80 mg treatment arms

At Week 48, AIMS mean score CFB for 80 mg and 40 mg groups were **-4.8 and -3.0,** respectively

At end of DBPC: **P<0.01; ***P<0.001 vs. placebo (statistical significance met for 80 mg/day based on the predefined fixed-sequence testing procedure); results based on least squares mean change from DBPC baseline using a mixed-effects model for repeated measures.
VE and drug-free follow-up periods: results based on arithmetic mean changes, with no imputation for missing values or significance testing between dose groups.
AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; DBPC, double-blind placebo-controlled; ITT, intent-to-treat; SEM, standard error of the mean; VBZ, valbenazine; VE, valbenazine extension.
1. Factor SA, et al. *J Clin Psych*. 2017; Nov/Dec;78(9):1344-1350. 2. Marder SR, et al. ACNP 2017; Atlanta, GA.

KINECT 4: AIMS Mean Score Change from Baseline by Visit



40 mg, n	45	33	30	25	20	20	20
80 mg, n	107	105	97	87	79	74	74

AIMS results based on investigator ratings indicated **mean improvement** during treatment and **returned toward baseline levels** after treatment withdrawal (Week 52)

40 mg: never had a dose increase to 80 mg; 80 mg: received 40 mg and increased to 80 mg, without a subsequent dose reduction. Data not shown for 11 participants who had a dose reduction from 80 mg/day to 40 mg/day after Week 4.
AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; SEM, standard error of the mean.
Marder SR, et al. ACNP Congress 2017; Palm Springs, CA.

KINECT 3 Extension & KINECT 4: Safety Results

	KINECT 3 Extension[1]		KINECT 4[2]	
	Post Week 6 – Week 48		Post Week 4 – Week 48	
	Valbenazine 40 mg (n=97)	Valbenazine 80 mg (n=101)	Valbenazine 40 mg (n=35)	Valbenazine 80 mg (n=107)
Any TEAE	62%	76%	63%	62%
Any TEAE Leading to Discontinuation	13%	18%	20%	10%
Any Serious TEAE	13%	16%	9%	16%
TEAE by MedDRA preferred term[a]				
Headache	7%	7%	9%	8%
Urinary tract infection	6%	7%	6%	6%
Diarrhea	3%	8%		
Dizziness	4%	7%		
Suicidal ideation	5%	5%		
Depression	6%	2%		

[a]TEAEs reported in ≥ 5% of participants in either treatment group.
[Blank], not reported/measured; AE, adverse event; TEAE, treatment-emergent AE.
1. Factor SA, et al. *J Clin Psych*. 2017; Nov/Dec;78(9):1344-1350. 2. Marder SR, et al. ACNP 2017; Atlanta, GA.

Long-Term Valbenazine & Deutetrabenazine Clinical Trials: Deutetrabenazine Open-Label Long-Term Trial

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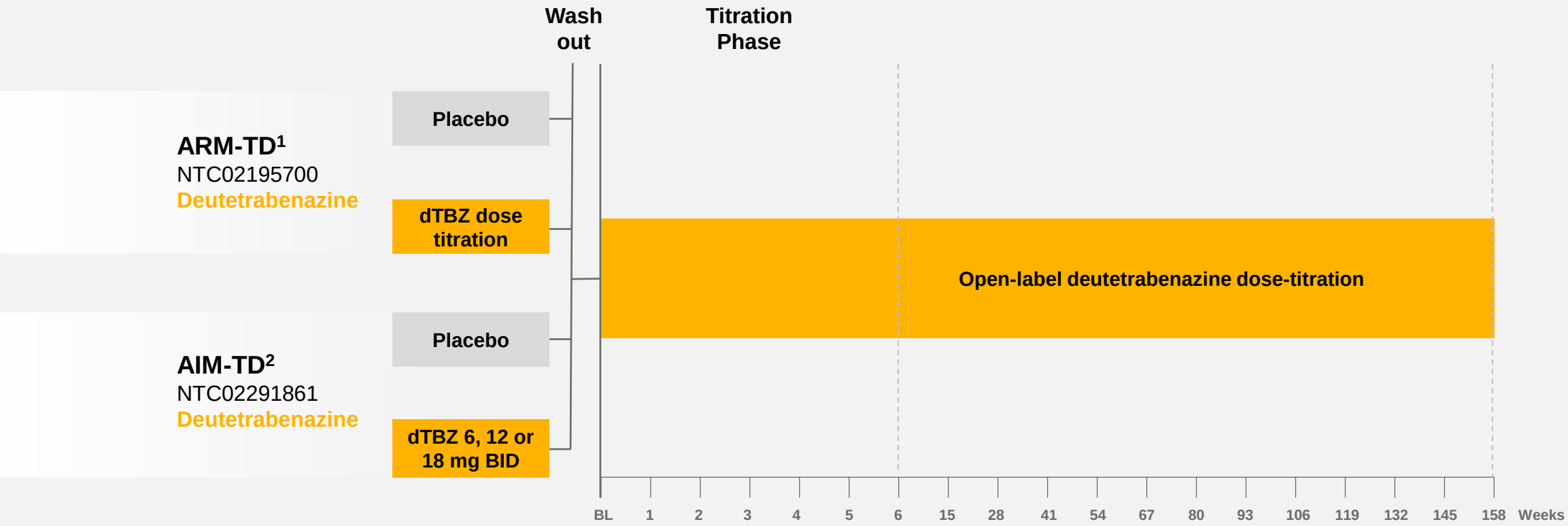
Deutetrabenazine Open-Label Long-Term Trial: Study Design



ARM-TD, Aim to Reduce Movements in Tardive Dyskinesia; BL, baseline; dTBZ, deutetrabenazine; BID, twice a day.

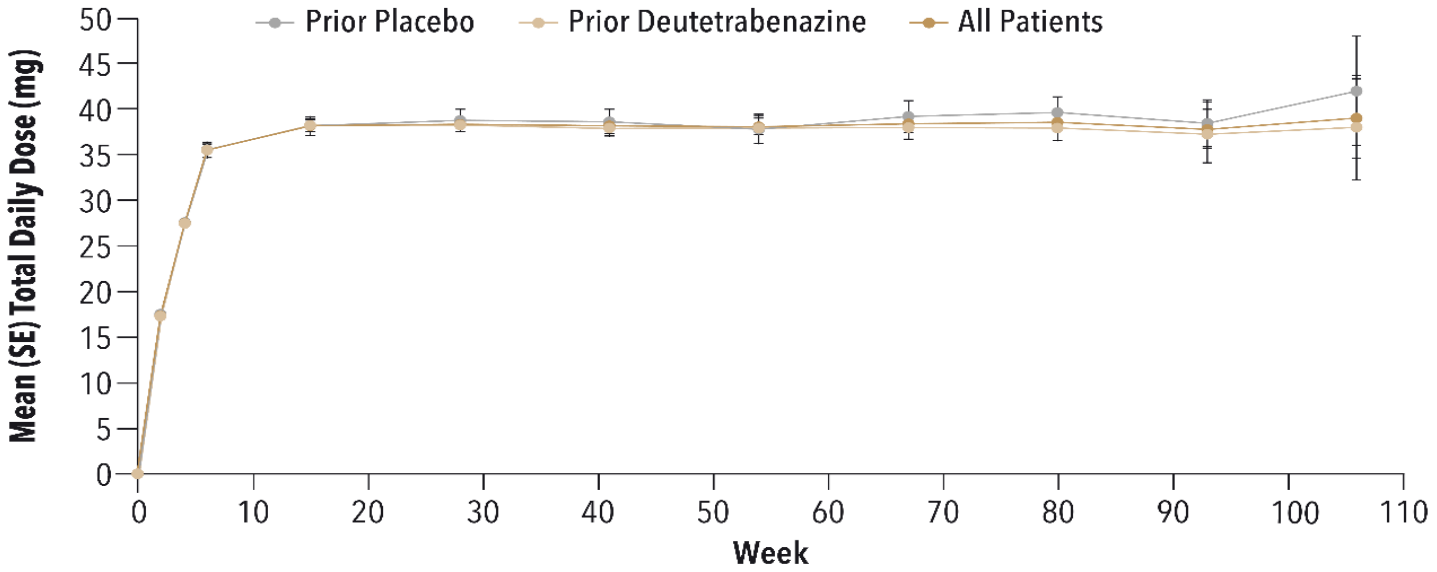
1. Anderson K, et al. Psych Congress 2017; New Orleans, LA. 2. Hauser RA, et al. AAN 2018; Los Angeles, CA.

Deutetrabenazine Open-Label Long-Term Trial: Baseline Characteristics

	Deutetrabenazine Open-Label Long-Term Study		
	Prior Placebo (n=111)	Prior dTBZ (n=232)	All Subjects in OLE (n=343)
Age, mean years (SE)	54.6 (1.1)	57.6 (0.7)	56.7 (0.6)
Female, n (%)	61 (55)	130 (56)	191 (56)
White, n (%)	88 (79)	182 (78)	270 (79)
TD duration (years), mean (SE)	6.1 (0.5)	5.5 (0.4)	5.7 (0.3)
Receiving DRBA at baseline, n (%)	86 (77)	170 (73)	256 (75)
Schizophrenia/schizoaffective disorder, n (%)	66 (59)	139 (60)	205 (60)
Mood disorder, n (%)[a]	44 (40)	93 (40)	137 (40)

[a]Bipolar disorder, depression, other.
dTBZ, deutetrabenazine; OLE, open-label extension; DRBA, dopamine receptor blocking agent.
Hauser RA, et al. AAN 2018; Los Angeles, CA.

Deutetrabenazine Open-Label Long-Term Trial: Average Daily Dose

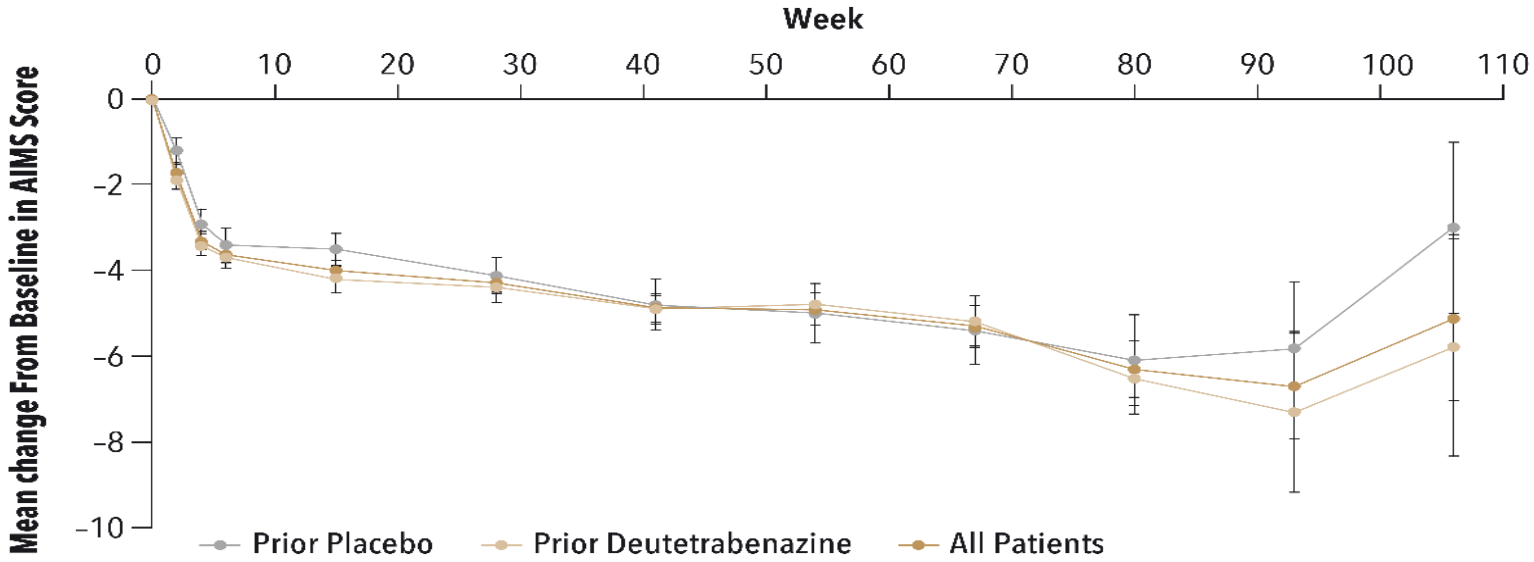


Week	0	2	4	6	15	28	41	54	67	80	93	106
Prior Placebo (n)	111	111	108	104	95	78	62	47	32	27	10	2
Prior Deutetrabenazine (n)	232	228	226	220	204	160	132	94	67	39	13	6
All Patients (n)	343	339	334	324	299	238	194	141	99	66	23	8

At Week 106, mean total daily dose was approximately 39.0 mg for all participants, 37.5 mg for participants who received prior dTBZ, and 42.5 mg for prior placebo

Table represents n values over the study period.
dTBZ, deutetrabenazine.
Hauser RA, et al. AAN 2018; Los Angeles, CA.

Deutetrabenazine Open-Label Long-Term Trial: Effectiveness Data



Week	0	2	4	6	15	28	41	54	67	80	93	106
Prior Placebo (n)	111	111	108	104	101	83	65	50	34	27	10	2
Prior Deutetrabenazine (n)	232	230	229	223	208	168	137	96	69	39	13	6
All Patients (n)	343	341	337	327	309	251	202	146	103	66	23	8

At Week 106, mean improvement in AIMS score was approximately -5.0 for all participants, -5.8 for participants who received prior dTBZ, and -3.0 for prior placebo

Table represents n values over the study period
dTBZ, deutetrabenazine.
Hauser RA, et al. AAN 2018; Los Angeles, CA.

Deutetrabenazine Open-Label Long-Term Trial: Safety Results at Year 2

	All Participants in Open-Label Extension Study (N=343)	
	Exposure-Adjusted Incidence Rate (# of participants/participants-years)	% of Participants
Any AEs	1.68 (233/138.4)	67.9%
Serious AEs	0.15 (45/308.3)	13.1%
Severe AEs	0.12 (37/311.6)	10.8%
Treatment-related AEs	0.12 (37/311.6)	10.8%
AEs leading to dose reduction	0.17 (48/290.1)	14.0%
AEs leading to dose suspension	0.06 (20/318.2)	5.8%
AEs leading to study withdrawal	0.08 (26/329.4)	7.6%
Headache	0.07 (23/309.7)	6.7%
Somnolence	0.09 (29/309.7)	8.5%
Depression	0.09 (27/314.0)	7.9%
Anxiety	0.09 (29/311.0)	8.5%
Suicidality	0.02 (7/328.6)	2.0%
Akathisia and restlessness	0.02 (5/328.1)	1.5%
Somnolence and sedation	0.11 (34/308.0)	9.9%
Parkinsonism	0.05 (15/319.8)	4.4%

AE, adverse event.

Fernandez HH, et al. AAN 2018; Los Angeles, CA.

Prescribing Information

Use navigation buttons on the right to see specific sections

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CONTRAINDICATIONS
WARNING & PRECAUTIONS & ADVERSE REACTIONS
DRUG INTERACTIONS
USE IN SPECIFIC POPULATIONS
MOA & BINDING AFFINITY

Prescribing Information: Summary

	Valbenazine[1]	Deutetrabenazine[2]
Indication & Usage	VMAT2 inhibitor for the treatment of adults with: • TD • Chorea associated with HD	VMAT2 inhibitor for the treatment of adults with: • TD • Chorea associated with HD
Boxed Warning	• Risk of depression and suicidality in HD	• Risk of depression and suicidality in HD
Dosing & Administration	• Initial dosage is 40 mg QD; after 1 week, increase to recommended dosage of 80 mg QD • A dosage of 40 mg or 60 mg QD may be considered depending on response and tolerability • Can be taken with or without food	• Initial dose is 12 mg/day; titrate by 6 mg/day weekly to a maximum recommended dose of 48 mg/day • dTBZ: Administer with food • dTBZ XR: Administer with or without food • Swallow tablets whole; do not chew, crush or break • Switching from TBZ to dTBZ: discontinue TBZ and initiate dTBZ the following day; follow the recommended conversion table in the PI

Other dosage recommendations

Valbenazine[1]	
Moderate or severe hepatic impairment	40 mg QD
Poor CYP2D6 metabolizers	
Strong CYP3A4 inhibitors	
Strong CYP2D6 inhibitors	
Strong CYP3A4 inducers	Concomitant use is not recommended

Deutetrabenazine[2]	
Poor CYP2D6 metabolizers	Should not exceed 36 mg/day (maximum single dose of 18 mg)
Strong CYP2D6 inhibitors	

BID, twice daily; dTBZ, deutetrabenazine; HD. Huntington's disease; PI, prescribing information; QD, once daily; TBZ, tetrabenazine; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc. 2. AUSTEDO [package Insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.

Prescribing Information: Contraindications

Contraindications

Valbenazine[1]	Deutetrabenazine[2]
• History of **hypersensitivity** to valbenazine or any components of valbenazine • Rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the face, lips, and mouth) have been reported	• **Suicidal** or untreated or inadequately treated **depression** in HD • **Hepatic impairment** • **Taking reserpine**: wait for ≥20 days after stopping reserpine before starting dTBZ • **Taking MAOIs**: should not be used in combination with MAOI, or within 14 days of discontinuing an MAOI • **Taking tetrabenazine or valbenazine**

HD. Huntington's disease; MAOI, monoamine oxidase inhibitor.

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc. 2. AUSTEDO [package Insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.

Prescribing Information: Warnings & Precautions and Adverse Reactions

	Valbenazine[1]	Deutetrabenazine[2]

Warnings & Precautions	• **Depression and suicidality** in patients with HD
	• **Hypersensitivity**, including angioedema may occur
	  • Discontinue if this occurs
	• **Somnolence/sedation:** may impair patient's ability to drive or operate hazardous machinery
	• **QT prolongation:** may cause an increase in QT interval
	  • Avoid use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval
	• **Neuroleptic malignant syndrome:** discontinue if this occurs.
	• **Parkinsonism:** cases of Parkinson-like symptoms (some severe), have been reported
	  • Reduce the dose or discontinue valbenazine in patients who develop clinically significant Parkinson-like signs or symptoms
		• **Depression and suicidality** in patients with HD
		• **Clinical worsening** and AEs in patients with HD
		• **QTc prolongation**
		  • Avoid use in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias
		• **Neuroleptic malignant syndrome:** discontinue dTBZ if this occurs
		• **Akathisia, agitation and restlessness:** reduce the dose or discontinue dTBZ if this occurs
		• **Parkinsonism:** dTBZ may cause parkinsonism in patients with HD or TD
		  • If patient develops parkinsonism during dTBZ treatment, the dTBZ dose should be reduced
		  • Some patients may require dTBZ discontinuation
		• **Sedation/somnolence:** may impair patient's ability to drive or operate complex machinery
		• **Hyperprolactinemia**
		• **Binding to melanin-containing tissues**

Adverse Reactions	• **Somnolence** is the most common adverse reaction (≥ 5% and twice the rate of placebo) • Other adverse reactions (≥2% and >placebo) include anticholinergic effects, balance disorders/fall, headache, akathisia, vomiting, nausea, arthralgia	• **Somnolence, diarrhea, dry mouth,** and **fatigue** were the most common adverse reactions (>8% and >placebo) in patients with HD[a] • **Nasopharyngitis** and **insomnia** were the most common adverse reactions (4% and >placebo) in patients with TD[a]

[a]In controlled clinical studies.

AE, adverse event; dTBZ, deutetrabenazine; HD, Huntington's Disease; TD, tardive dyskinesia.

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc. 2. AUSTEDO [package Insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.

Prescribing Information: Adverse Reactions from TD Studies

Adverse Reaction[a]	Valbenazine[1] (n=262)	Placebo (n=183)
Somnolence (somnolence, fatigue, sedation)	10.9%	4.2%
Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)	5.4%	4.9%
Balance disorders/fall (fall, gait disturbance, dizziness, balance disorder)	4.1%	2.2%
Headache	3.4%	2.7%
Akathisia (akathisia, restlessness)	2.7%	0.5%
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%
Arthralgia	2.3%	0.5%

Adverse Reaction[b]	Deutetrabenazine[2] (n=279)	Placebo (n=131)
Nasopharyngitis	4%	2%
Insomnia	4%	1%
Depression/Dysthymic disorder	2%	1%
Akathisia/Agitation/Restlessness	2%	1%

[a]Adverse Reactions in 3 Placebo-Controlled TD Studies of 6-week Treatment Duration Reported at ≥2% and >Placebo.
[b]Adverse Reactions in 2 Placebo-Controlled TD Studies of 12-week Treatment Duration Reported at ≥2% and >Placebo.

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Prescribing Information: Drug Interactions

	Valbenazine[1]	Deutetrabenazine[2]
MAOIs	Avoid concomitant use with MAOIs, or within 14 days of discontinuing therapy with an MAOI	Should not be used in combination with MAOI, or within 14 days of discontinuing therapy with an MAOI
Strong CYP3A4 inhibitors	Reduce valbenazine dose to 40 mg	N/A
Strong CYP2D6 inhibitors	Reduce valbenazine dose to 40 mg	• Reduction in dTBZ dose may be necessary • Daily dose of dTBZ should not exceed 36 mg/day (maximum single dose of 18 mg)
Strong CYP3A4 inducers	Concomitant use not recommended	N/A
Digoxin	Digoxin concentration should be monitored • Increasing digoxin exposure may increase the risk of exposure related adverse reactions • Dosage adjust of digoxin may be necessary	N/A
Drugs that cause QTc Prolongation	May cause an increase in QTc interval	May increase the risk of the occurrence of torsade de pointes and/or sudden death
Reserpine	N/A	Prescribers should wait for chorea or dyskinesia to reemerge before administering dTBZ to help reduce risk of overdosage and major depletion of serotonin and norepinephrine in CNS
Neuroleptic drugs	N/A	Increase risk of parkinsonism, NMS, and akathisia
Alcohol or other sedating drugs	N/A	May have additive effects and worsen sedation and somnolence
TBZ or VBZ	N/A	Contraindicated in participants currently taking TBZ or VBZ • dTBZ may be initiated the day following TBZ discontinuation

CNS, central nervous system; dTBZ, deutetrabenazine; MAOI, monoamine oxidase inhibitor; NMS, neuroleptic malignant syndrome; TBZ, tetrabenazine; VBZ, valbenazine.

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Prescribing Information: Use in Specific Populations

	Valbenazine[1]	Deutetrabenazine[2]
Pregnancy	May cause fetal harm[a]	May cause fetal harm[a]
Lactation	Advise not to breastfeed	Consider benefits of breastfeeding along with the mother's need for dTBZ and potential adverse effects on the infant
Pediatric	Safety and effectiveness not established	Safety and effectiveness not established
Geriatric	No dose adjustment required in elderly	Dose selection for an elderly patient should be cautious, usually starting at the lower end of the dose range, given higher rates of hepatic, renal, and cardiac dysfunction, and concomitant disease or other drug therapy
CYP2D6 Poor Metabolizers	Recommended dosage: 40 mg QD	Should not exceed 36 mg/day (maximum single dose of 18 mg)
Hepatic Impairment	Moderate to severe: reduce dose to 40 mg QD	Contraindicated
Renal Impairment	No dose adjustment necessary for mild, moderate, or severe renal impairment	N/A

[a]Based on animal data.
dTBZ, deutetrabenazine; QD, once daily.
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Prescribing Information: MOA and Binding Affinity

	Valbenazine[1]	Deutetrabenazine[2]
MOA	• MOA in the treatment of TD is unclear • Thought to be mediated through the reversible inhibition of VMAT2, a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release	• MOA in the treatment of TD is unknown • Believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals • The major circulating metabolites of dTBZ (a-HTBZ and b-HTBZ) are reversible inhibitors of VMAT2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores
Binding Affinity	• Valbenazine inhibits human VMAT2 with no appreciable binding affinity for VMAT1 • Valbenazine and its active metabolite ([+]-α-HTBZ) have no appreciable binding affinity for dopaminergic (including D2), serotonergic (including 5HT2B), adrenergic, histaminergic or muscarinic receptors	• **Melanin binding:** dTBZ or its metabolites bind to melanin-containing tissues (i.e., eye, skin, fur) in pigmented rats. • After a single oral dose of radiolabeled dTBZ, radioactivity was still detected in eye and fur at 35 days following dosing

5HT2B, 5-Hydroxytryptamine receptor 2B; dTBZ, deutetrabenazine; HTBZ, dihydrotetrabenazine; MOA, mechanism of action; TD, tardive dyskinesia; VBZ, valbenazine; VMAT, vesicular monoamine transporter.

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