Indirect Treatment Comparison (ITC) of Valbenazine and Deutetrabenazine for the Treatment of Adults With Tardive Dyskinesia

Aggarwal S et al. *Journal of Comparative Effectiveness Research*. 2019;8(13):1077-1088.

NEUROCRINE® BIOSCIENCES

Table of Contents

Background on Indirect Treatment Comparisons (ITC)

Well-designed and implemented head-to-head RCTs are generally considered to provide the most rigorous and valid research evidence on the relative effects of therapeutic interventions.[1] Evidence from head-to-head RCTs is often limited or unavailable. Indirect treatment comparisons are developed using data obtained by a systematic review in the absence of a head-to-head clinical trial and are not meant to imply that a clinical trial with active comparators was completed. The intended audience for this type of analysis is generally health economics and outcomes focused. As such, there are limitations due to the lack of head-to-head data inherent in any indirect treatment comparison and should be considered when evaluating the data.

RCT=randomized controlled clinical trial

References: 1. Song F, et al. *BMJ*. 2009 Apr;338:b1147.

Indirect Treatment Comparison: Definition

- **Purpose:** When there are no head-to-head data available, ITCs are used to compare treatments through treatment effects adjusted to a common comparator (often placebo)[1,2]
- **Indirect comparison** refers to a comparison of different treatment options using data from **separate studies**, in contrast to a **direct comparison** within **randomized controlled trials (RCTs)**[1]

References: 1. Song F et al. *BMJ*. 2011;343:d4909. 2. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

Indirect Treatment Comparison: Overview of Methodology

- All relevant studies must be identified during a literature search and populations must be homogeneous to aggregate[1,2]
  - A common comparator (such as placebo), and data from both treatments are compared[1,2]
  - Point estimates (and their standard errors/confidence intervals [CIs]) are used in a series of equations [Bucher methodology[2]] to get an indirect comparison
  - Data for each comparator used in an ITC must be combined in a meta-analysis if more than one study is used for each treatment option[1,2]

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Checklist can be used to ensure all the requirements of an ITC study are met[1]

References: 1. Hoaglin DC et al. *Value Health.* 2011;14(4):429-437. 2. Bucher HC et al. *J Clin Epidemiol.*1997;50:683-691.

ITC Is Only Feasible if Similar Trials Are Analyzed in Respect to Treatment Effect

Proper ITC

- ☑ Same comparator across trials (placebo)
- ☑ Comparable:
  - Study population
  - Design
  - Outcome measures
  - Trials
- ☑ No relevant heterogeneity between trial results in pairwise comparisons
- ☑ No discrepancy between direct and indirect evidence
- ☑ Use statistical method to preserve study randomization (Bucher method)

Incorrect ITC

- ☒ Different comparator (compared against placebo vs against standard of care)
- ☒ Trial data violates assumption of similarity
- ☒ Different study populations
- ☒ Different design or outcomes measures
- ☒ High heterogeneity score
- ☒ Discrepancies between direct and indirect evidence
- ☒ Poor quality studies included (not a full literature search and meta-analysis; independent/duplicate)

- Indirect comparison method limitations[1,2]
  - As noted by Bucher, the strength of inference from indirect comparisons is limited
  - This method can only be applied to data generated from 2-arm trials involving simple indirect comparison of 3 treatments (including common comparator)

References: 1. Bucher HC et al. *J Clin Epidemiol*. 1997;50:683-691. 2. Tonin FS et al. *Pharm Pract*. 2017;15(1):943.

Indirect Treatment Comparison: Key Takeaways

- ITCs are:
  - ☑ Useful in the absence of direct head-to-head trials[1]
  - ☑ A way to compare 2 drugs that have a common comparator (often placebo)[1]
  - ☑ Largely used for inputs into economic models and clinical comparisons for HTA agencies[2]

- In a meta-analysis comparing direct and indirect comparisons, the majority of indirect treatment comparisons did not have statistically significant results[1]

If the results of an ITC show statistically significant differences in endpoints between comparators, this suggests a difference in efficacy[3,4]

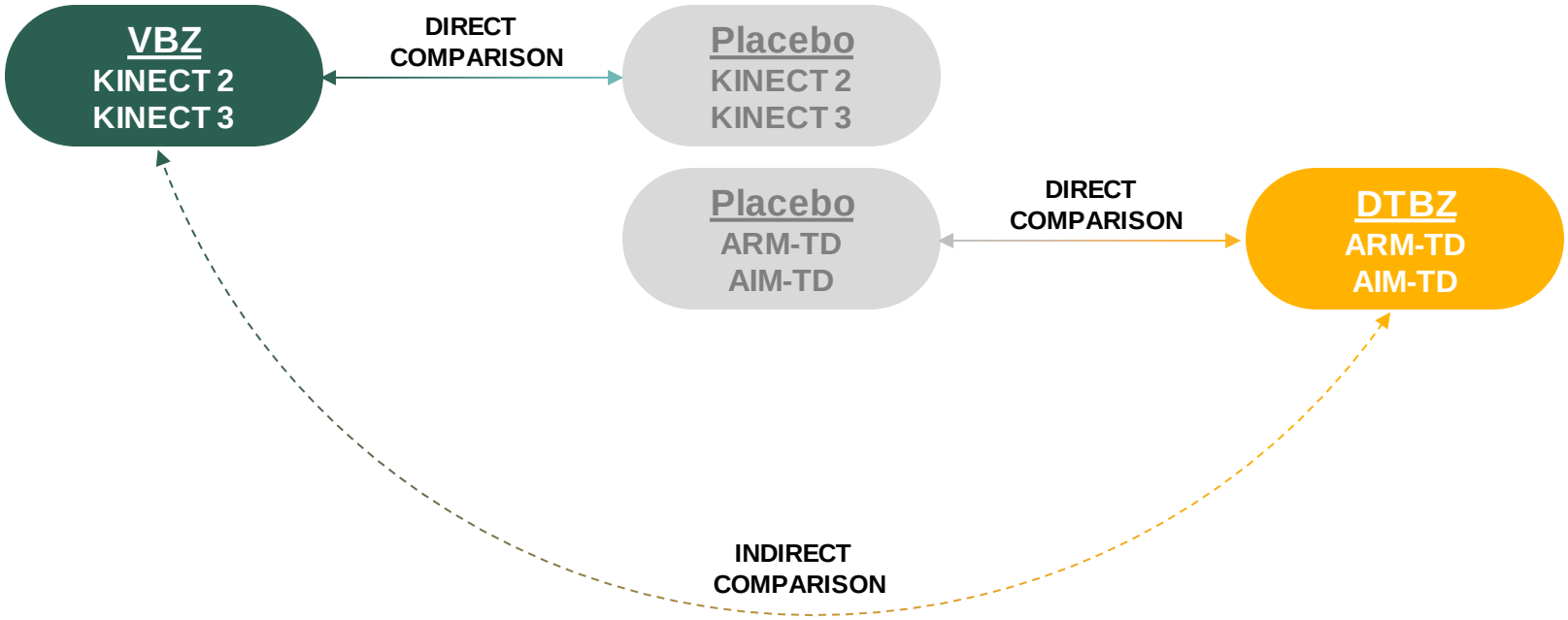
References: 1. Song F et al. *BMJ*. 2011;343:d4909 doi: 10.1136/bmj.d4909. 2. Balijepalli C et al. https://www.evidera.com/wp-content/uploads/2018/10/03-Bucher-vs-Bayesian-NMA-Approaches_Fall2018.pdf. Accessed July 2, 2020. 3. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088. 4. Lorenzi M et al. *J Drug Assess*. 2019;8(1):135-145.

ITC of Valbenazine and Deutetrabenazine: Methodology

Methods

Objective: To assess the comparative efficacy and safety of valbenazine (VBZ) and deutetrabenazine (DTBZ)[2]

- Bucher method of indirect treatment comparison (ITC)[1]
- Double-blind, placebo-controlled studies (RCTs)



References: 1. Bucher HC et al. *J Clin Epidemiol*.1997;50:683-691. 2. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

ITC of Valbenazine and Deutetrabenazine: Pivotal Trial Similarities and Differences

KINECT 2, KINECT 3, ARM-TD, and AIM-TD: Baseline Characteristics

TRIAL DIFFERENCES

Study	Age, Mean (SD)	Female, n (%)	White, n (%)	AIMS Score, Mean (SD)	Schizophrenia/ Schizoaffective Disorder, n (%)
Valbenazine					
KINECT 2[1]					
Placebo	55.6 (9.8)	22 (44.9)	30 (61.2)	7.9 (4.5)	30 (61.2)
Valbenazine	56.7 (10.8)	21 (41.2)	33 (64.7)	8.0 (3.5)	28 (54.9)
All	56.2 (10.3)	43 (43.0)	63 (63.0)	8.0 (4.0)	58 (58.0)
KINECT 3[2]					
Placebo	57.0 (10.5)	34 (44.7)	43 (56.6)	9.9 (4.3)	50 (65.8)
Valbenazine 40 mg	55.3 (8.5)	30 (41.7)	41 (56.9)	9.7 (4.1)	48 (66.7)
Valbenazine 80 mg	56.0 (10.1)	40 (50.6)	44 (55.7)	10.4 (3.6)	52 (65.8)
All	56.1 (9.7)	104 (45.8)	128 (56.4)	10.0 (4.0)	150 (66.1)
Deutetrabenazine					
ARM-TD[3]					
Placebo	53.3 (10.6)	32 (54.2)	44 (74.6)	9.6 (3.8)	40 (67.8)
Deutetrabenazine	55.9 (9.8)	29 (50.0)	37 (63.8)	9.6 (4.1)	40 (69.0)
All	54.6 (10.3)	61 (52.1)	81 (69.2)	9.6 (3.9)	80 (68.4)
AIM-TD[4]					
Placebo	54.6 (12.1)	37 (51)	59 (82)	9.5 (2.7)*	42 (58.3)
Deutetrabenazine 12 mg	57.0 (10.0)	42 (57)	58 (78)	9.6 (2.4)*	40 (54.1)
Deutetrabenazine 24 mg	55.6 (11.3)	41 (56)	54 (74)	9.4 (2.9)*	49 (67.1)
Deutetrabenazine 36 mg	58.3 (11.6)	42 (57)	61 (82)	10.1 (3.2)*	44 (59.5)
All	56.4 (11.3)	162 (55)	232 (79)	NR*	175 (59.7)

*Based on the efficacy population. All other results based on safety populations.
NR=not reported; SD=standard deviation.

References: 1. O'Brien CF et al. *Mov Disord.* 2015;30(12):1681-1687. 2. Hauser RA et al. *Am J Psychiatry.* 2017;174(5):476-484. 3. Fernandez HH et al. *Neurology.* 2017;88(21):2003-2010. 4. Anderson KE et al. *Lancet Psychiatry.* 2017;4(8):595-604.

KINECT 2, KINECT 3, ARM-TD, and AIM-TD: Baseline Characteristics

TRIAL DIFFERENCES

Study	Age, Mean (SD)	Female, n (%)	White, n (%)	AIMS Score, Mean (SD)	Schizophrenia/ Schizoaffective Disorder, n (%)
Valbenazine					
KINECT 2[1]					
Placebo	55.6 (9.8)	22 (44.9)		(4.5)	30 (61.2)
Valbenazine	56.7 (10.8)	21 (41.2)		(3.5)	28 (54.9)
All	56.2 (10.3)	43 (43.0)		(4.0)	58 (58.0)
KINECT 3[2]					
Placebo	57.0 (10.5)	34 (44.7)		(4.3)	50 (65.8)
Valbenazine 40 mg	55.3 (8.5)	30 (41.7)		(4.1)	48 (66.7)
Valbenazine 80 mg	56.0 (10.1)	40 (50.6)		(3.6)	52 (65.8)
All	56.1 (9.7)	104 (45.8)		(4.0)	150 (66.1)
Deutetrabenazine					
ARM-TD[3]					
Placebo	53.3 (10.6)	32 (54.2)	44 (74.6)	9.6 (3.8)	40 (67.8)
Deutetrabenazine	55.9 (9.8)	29 (50.0)	37 (63.8)	9.6 (4.1)	40 (69.0)
All	54.6 (10.3)	61 (52.1)	81 (69.2)	9.6 (3.9)	80 (68.4)
AIM-TD[4]					
Placebo	54.6 (12.1)	37 (51)	59 (82)	9.5 (2.7)*	42 (58.3)
Deutetrabenazine 12 mg	57.0 (10.0)	42 (57)	58 (78)	9.6 (2.4)*	40 (54.1)
Deutetrabenazine 24 mg	55.6 (11.3)	41 (56)	54 (74)	9.4 (2.9)*	49 (67.1)
Deutetrabenazine 36 mg	58.3 (11.6)	42 (57)	61 (82)	10.1 (3.2)*	44 (59.5)
All	56.4 (11.3)	162 (55)	232 (79)	NR*	175 (59.7)

Slightly lower proportion of females

*Based on the efficacy population. All other results based on safety populations.
NR=not reported; SD=standard deviation.

References: 1. O'Brien CF et al. *Mov Disord.* 2015;30(12):1681-1687. 2. Hauser RA et al. *Am J Psychiatry.* 2017;174(5):476-484. 3. Fernandez HH et al. *Neurology.* 2017;88(21):2003-2010. 4. Anderson KE et al. *Lancet Psychiatry.* 2017;4(8):595-604.

KINECT 2, KINECT 3, ARM-TD, and AIM-TD: Baseline Characteristics

TRIAL DIFFERENCES

Study	Age, Mean (SD)	Female, n (%)	White, n (%)	AIMS Score, Mean (SD)	Schizophrenia/ Schizoaffective Disorder, n (%)
Valbenazine					
KINECT 2[1]					
Placebo	55.6 (9.8)	22 (44.9)	30 (61.2)		61.2)
Valbenazine	56.7 (10.8)	21 (41.2)	33 (64.7)		54.9)
All	56.2 (10.3)	43 (43.0)	63 (63.0)		58.0)
KINECT 3[2]					
Placebo	57.0 (10.5)	34 (44.7)	43 (56.6)		65.8)
Valbenazine 40 mg	55.3 (8.5)	30 (41.7)	41 (56.9)		66.7)
Valbenazine 80 mg	56.0 (10.1)	40 (50.6)	44 (55.7)		65.8)
All	56.1 (9.7)	104 (45.8)	128 (56.4)		66.1)
Deutetrabenazine					
ARM-TD[3]					
Placebo	53.3 (10.6)	32 (54.2)	44 (74.6)	9.6 (3.8)	40 (67.8)
Deutetrabenazine	55.9 (9.8)	29 (50.0)	37 (63.8)	9.6 (4.1)	40 (69.0)
All	54.6 (10.3)	61 (52.1)	81 (69.2)	9.6 (3.9)	80 (68.4)
AIM-TD[4]					
Placebo	54.6 (12.1)	37 (51)	59 (82)	9.5 (2.7)*	42 (58.3)
Deutetrabenazine 12 mg	57.0 (10.0)	42 (57)	58 (78)	9.6 (2.4)*	40 (54.1)
Deutetrabenazine 24 mg	55.6 (11.3)	41 (56)	54 (74)	9.4 (2.9)*	49 (67.1)
Deutetrabenazine 36 mg	58.3 (11.6)	42 (57)	61 (82)	10.1 (3.2)*	44 (59.5)
All	56.4 (11.3)	162 (55)	232 (79)	NR*	175 (59.7)

Larger proportion of non-white patients

*Based on the efficacy population. All other results based on safety populations.
NR=not reported; SD=standard deviation.

References: 1. O'Brien CF et al. *Mov Disord.* 2015;30(12):1681-1687. 2. Hauser RA et al. *Am J Psychiatry.* 2017;174(5):476-484. 3. Fernandez HH et al. *Neurology.* 2017;88(21):2003-2010. 4. Anderson KE et al. *Lancet Psychiatry.* 2017;4(8):595-604.

KINECT 2, KINECT 3, ARM-TD, and AIM-TD: Baseline Characteristics

TRIAL DIFFERENCES

Study	Age, Mean (SD)	Female, n (%)	White, n (%)	AIMS Score, Mean (SD)	Schizophrenia/ Schizoaffective Disorder, n (%)
Valbenazine					
KINECT 2[1]					
Placebo	55.6 (9.8)			7.9 (4.5)	30 (61.2)
Valbenazine	56.7 (10.8)			8.0 (3.5)	28 (54.9)
All	56.2 (10.3)			8.0 (4.0)	58 (58.0)
KINECT 3[2]					
Placebo	57.0 (10.5)			9.9 (4.3)	50 (65.8)
Valbenazine 40 mg	55.3 (8.5)			9.7 (4.1)	48 (66.7)
Valbenazine 80 mg	56.0 (10.1)			10.4 (3.6)	52 (65.8)
All	56.1 (9.7)			10.0 (4.0)	150 (66.1)
Deutetrabenazine					
ARM-TD[3]					
Placebo	53.3 (10.6)	32 (54.2)	44 (74.6)	9.6 (3.8)	40 (67.8)
Deutetrabenazine	55.9 (9.8)	29 (50.0)	37 (63.8)	9.6 (4.1)	40 (69.0)
All	54.6 (10.3)	61 (52.1)	81 (69.2)	9.6 (3.9)	80 (68.4)
AIM-TD[4]					
Placebo	54.6 (12.1)	37 (51)	59 (82)	9.5 (2.7)*	42 (58.3)
Deutetrabenazine 12 mg	57.0 (10.0)	42 (57)	58 (78)	9.6 (2.4)*	40 (54.1)
Deutetrabenazine 24 mg	55.6 (11.3)	41 (56)	54 (74)	9.4 (2.9)*	49 (67.1)
Deutetrabenazine 36 mg	58.3 (11.6)	42 (57)	61 (82)	10.1 (3.2)*	44 (59.5)
All	56.4 (11.3)	162 (55)	232 (79)	NR*	175 (59.7)

Mean baseline AIMS scores were slightly lower in KINECT 2 than in KINECT 3 or ARM-TD

*Based on the efficacy population. All other results based on safety populations.
NR=not reported; SD=standard deviation.

References: 1. O'Brien CF et al. *Mov Disord.* 2015;30(12):1681-1687. 2. Hauser RA et al. *Am J Psychiatry.* 2017;174(5):476-484. 3. Fernandez HH et al. *Neurology.* 2017;88(21):2003-2010. 4. Anderson KE et al. *Lancet Psychiatry.* 2017;4(8):595-604.

Pivotal Trial Data Supports Use of Indirect Comparison Analysis

- From the baseline characteristics, there were no significant differences between trials[1]
- Heterogeneity was assessed with the Cochrane Q and I^2 statistics for each analysis (with heterogeneity being indicated by a $P<0.05$ or $I^2 \geq 50\%$, respectively)[2]
  - I^2 is a statistic that indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity[3]
- The heterogeneity test of I^2 on AIMS mean score change from baseline demonstrated a score of 0% across both valbenazine and deutetrabenazine trials[2,4]

The trials chosen for this ITC are well aligned for this type of analysis

References: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088. 2. Solmi M et al. *Drug Des Devel Ther*. 2018;12:1215-1238. 3. Higgins JPT et al. *BMJ*. 2003;327(7414):557-560. 4. Data on file (Meta-analysis slide deck).

Study Designs of Pivotal Trials: Similar Study Design in the 4 RCTs—Valbenazine

Kinect 2[1]

NCT01733121

Treatment Groups, Dosage* (n)

- Flexible 25 mg-75 mg (44)
- Placebo (45)

n=89

6 Weeks

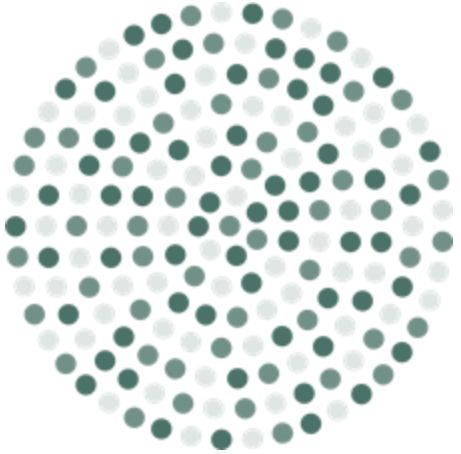
Kinect 3[2]

NCT02274558

Treatment Groups, Dosage* (n)

- 40 mg (52)
- 80 mg (61)
- Placebo (66)

n=179



6 Weeks

Key Eligibility Criteria/Methodology

- Drug-induced TD for ≥3 months
- **Moderate or severe tardive dyskinesia (as qualitatively assessed)†**
- Stable psychiatric status
- Stable doses of psychiatric medications allowed
- **Concomitant anticholinergics allowed**

Efficacy Outcomes

- AIMS total CFB
- AIMS 50% response
- CGIC response

Bolded lines indicate the differences between the valbenazine and deutetrabenazine trials.

*Dosages reported in total mg/day (valbenazine was given once daily and deutetrabenazine was given twice daily).
†Based on qualitative assessment of screening video by an external reviewer.
CFB=change from baseline; CGIC=Clinical Global Impression of Change.
References: 1. O'Brien CF et al. *Mov Disord.* 2015;30(12):1681-1687. 2. Hauser RA et al. *Am J Psychiatry.* 2017;174(5):476-484.

Study Designs of Pivotal Trials: Similar Study Design in the 4 RCTs—Deutetrabenazine

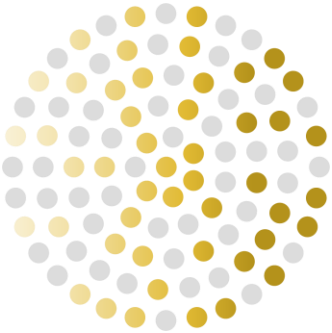
ARM-TD[1]

NCT02195700

Treatment Groups, Dosage* (n)

- Flexible 12 mg-48 mg (48)‡
- Placebo (49)

n=97



12 Weeks

AIM=TD[2]

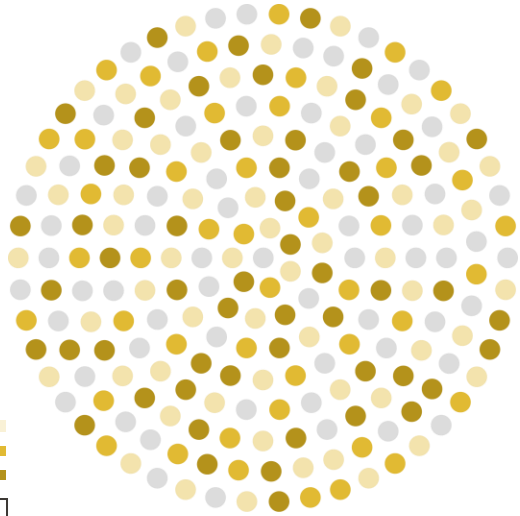
NTC02291861

Treatment Groups, Dosage* (n)

- 12 mg (60)
- 24 mg (49)
- 36 mg (55)
- Placebo (58)

n=222

12 Weeks



Key Eligibility Criteria/Methodology

- TD diagnosis
- **AIMS total score ≥6†**
- DRBA exposure ≥3 months (≥1 month if ≥60 years)
- Stable doses of psychiatric medications allowed
- **Strong anticholinergics not allowed**

Efficacy Outcomes

- AIMS total CFB
- AIMS response
- CGIC response

Bolded lines indicate the differences between the deutetrabenazine and valbenazine trials.

*Dosages reported in total mg/day (valbenazine was given once daily and deutetrabenazine was given twice daily).
‡At the end of the titration period the mean (SD) total daily dose was 38.8 (7.92) mg/day. At the end of the treatment period, the mean (SD) total daily dose was 38.3 (7.97) mg/day
†Investigator-assessed at both screening and baseline and confirmed by blinded central video rater.

References: 1. Fernandez HH, et al. *Neurology.* 2017;88(21):2003-2010. 2. Anderson KE, et al. *Lancet Psychiatry.* 2017;4(8):595-604.

Clinical and Safety Outcome Measures for Pivotal Trial Results

- **Efficacy Outcomes[1]:**
  - AIMS CFB (point improvement)
  - AIMS 50% response (ratio)
    - ≥50% total score improvement from baseline
  - CGIC response (ratio)
    - Score of 1 “very much improved,” or 2 “much improved”

- **Safety outcomes[1]:**
  - Treatment-emergent adverse event (TEAE)
  - TEAEs leading to discontinuation
  - Severe adverse events (SAEs)

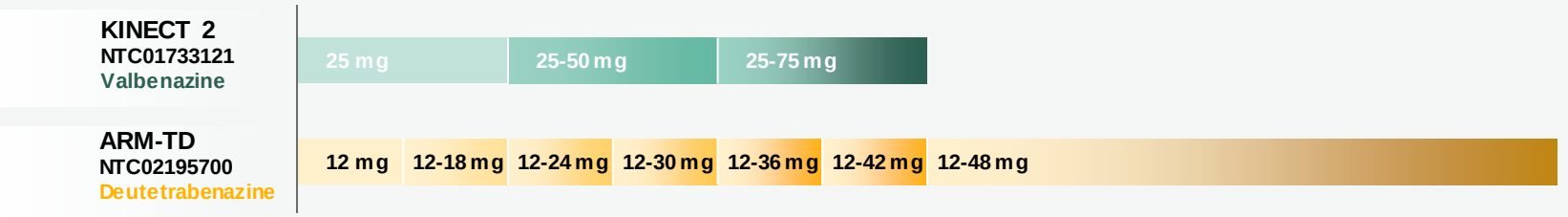
- **Subgroups[1]:**
  - At different timepoints (AIMS CFB)
  - Using pooled vs individual study arms (only KINECT 3 and AIM-TD)
  - Using only individual studies

Reference: 1. Aggarwal S et al. *J Comp Eff Res.* 2019;8(13):1077-1088.

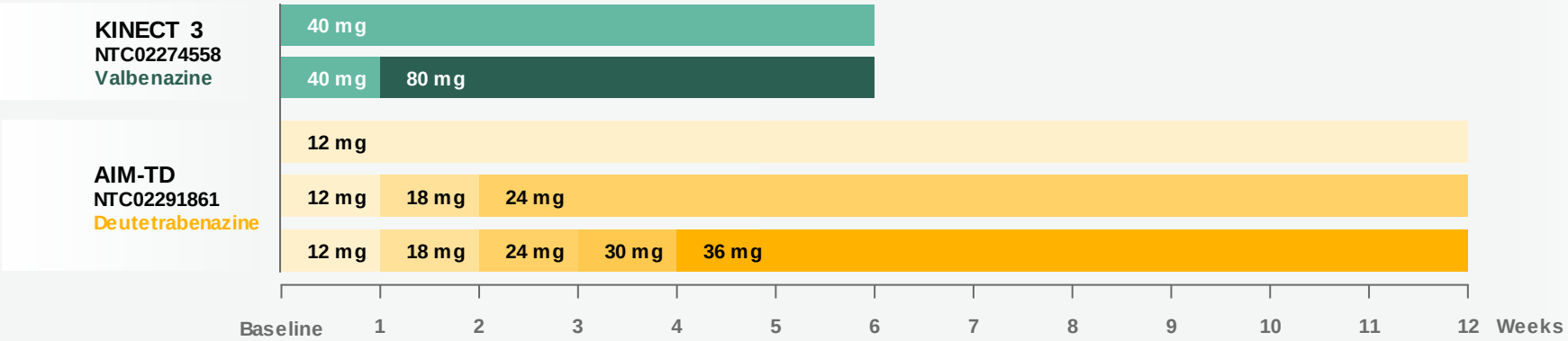
ITC of Valbenazine and Deutetrabenazine: Why Timing Matters

Indirect Treatment Comparison: 4 Pivotal Trials Had Different Dosing Schedules

Flexible Dose



Fixed Dose



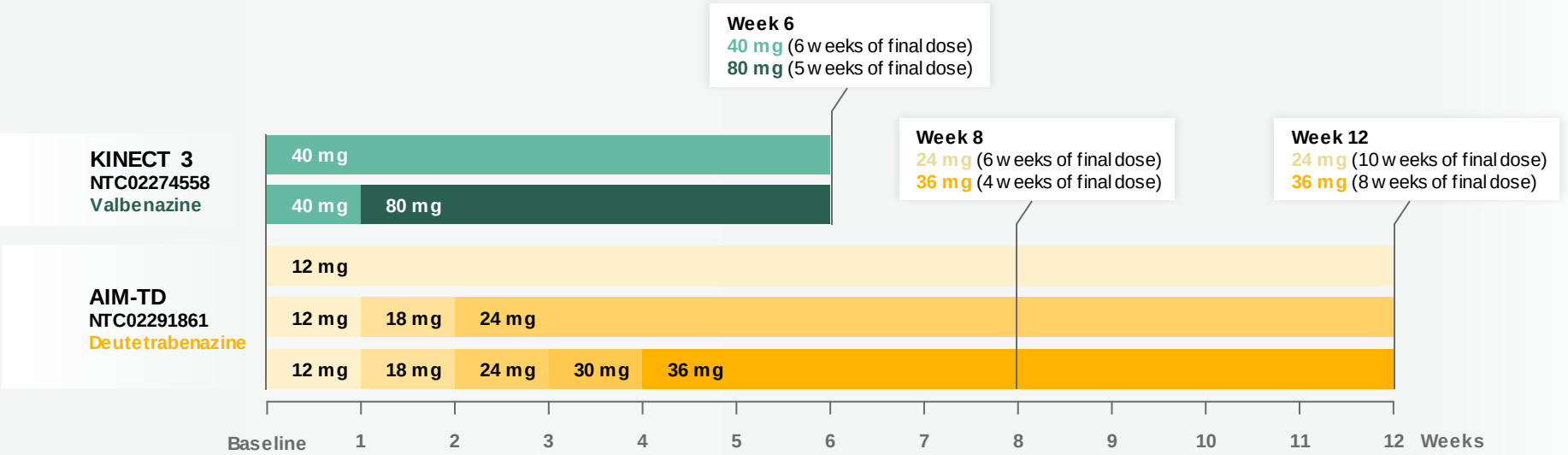
Reference: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

Indirect Treatment Comparison: Dose Comparison Methodology

Fixed dose studies were used to compare efficacy outcomes by dose (KINECT 3 and AIM-TD)

- Valbenazine (VBZ) 40 mg or 80 mg at Week 6
- Deutetrabenazine (DTBZ) 24 mg or 36 mg, Week 8 or Week 12

- Due to different dosing periods, comparable time points were analyzed from the studies
  - VBZ 6-week AIMS mean changes from baseline were compared to DTBZ Week 8 (AIM-TD) using a plot digitizer



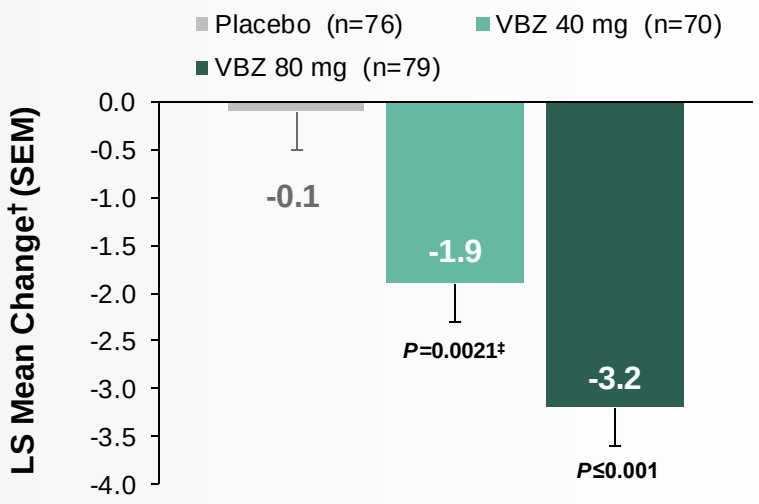
Reference: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

ITC of Valbenazine and Deutetrabenazine: Pivotal Trial Data

Primary Efficacy Outcome Data From Fixed-Dose Pivotal Trials

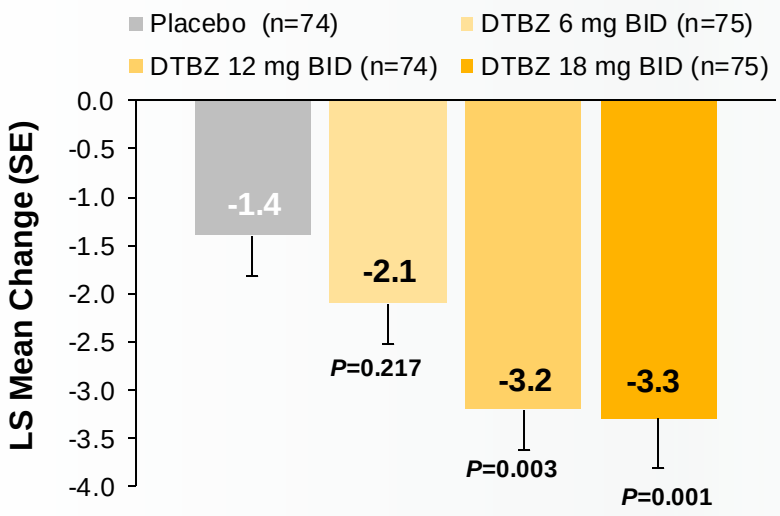
KINECT 3[1*]

AIMS Change From Baseline at **Week 6**
Primary Efficacy Endpoint



AIM-TD[2,§]

AIMS Change From Baseline at **Week 12**
Primary Efficacy Endpoint



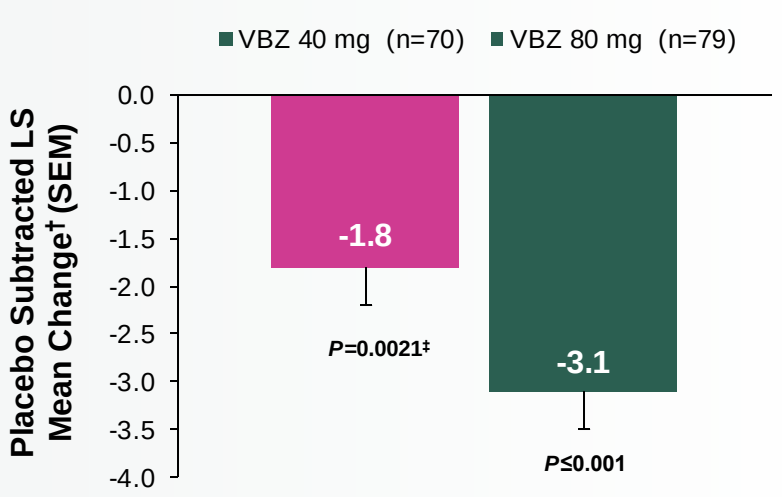
*Intent-to-treat (ITT): Included all randomized subjects who had at least one post-randomization AIMS value.
†Least squares (LS) mean based on the MMRM model, which includes baseline AIMS dyskinesia total score value as a covariate, and treatment group, disease category, visit, treatment group by visit, and baseline by visit interaction as fixed effects, and subject as a random effect.
‡Nominal *P*-value, statistical analysis plan-specified hierarchical analysis precluded testing 40 mg result for significance.
§Modified ITT: included all randomized subjects who had a baseline AIMS score of 6 or more with at least one post-baseline AIMS assessment.
AIMS=Abnormal Involuntary Movement Scale; BID=twice a day; SE=standard error; SEM=standard error of the mean.

References: 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.

Placebo Subtracted Efficacy Outcome Data from Fixed-Dose Pivotal Trials

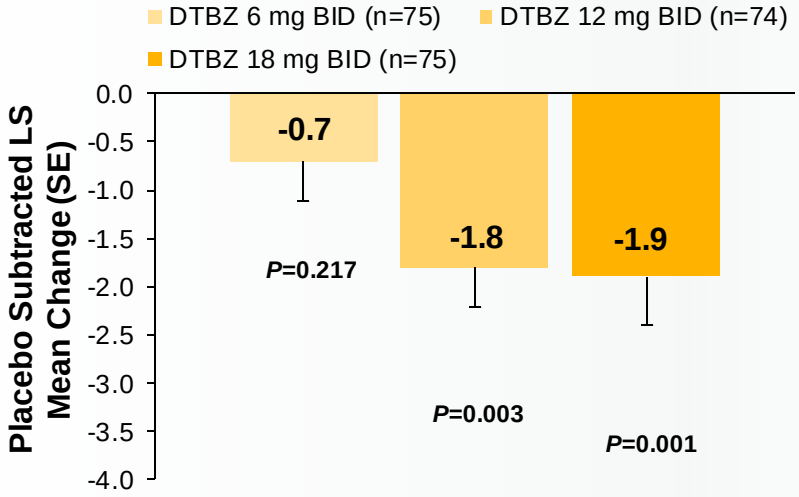
KINECT 3[1*]

AIMS Change From Baseline at **Week 6**
Primary Efficacy Endpoint



AIM-TD[2,§]

AIMS Change From Baseline at **Week 12**
Primary Efficacy Endpoint



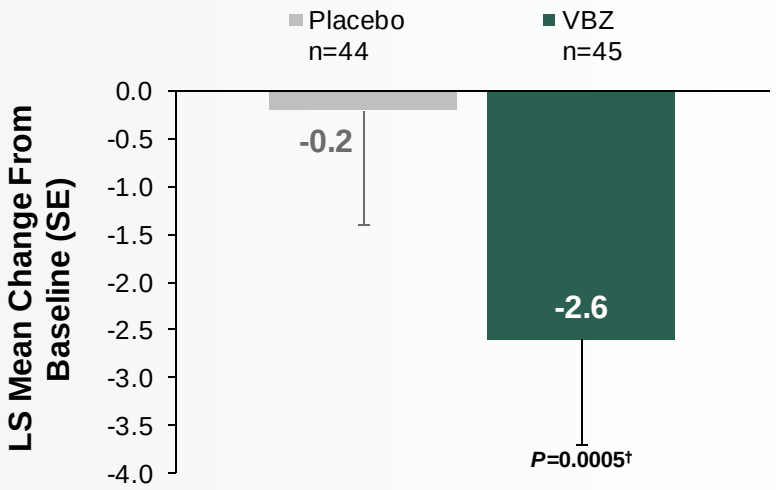
*ITT: Included all randomized subjects who had at least one post-randomization AIMS value.
†LS mean based on the MMRM model, which includes baseline AIMS dyskinesia total score value as a covariate, and treatment group, disease category, visit, treatment group by visit, and baseline by visit interaction as fixed effects, and subject as a random effect.
‡Nominal *P*-value, statistical analysis plan-specified hierarchical analysis precluded testing 40 mg result for significance.
§Modified ITT: included all randomized subjects who had a baseline AIMS score of 6 or more with at least one post-baseline AIMS assessment.

References: 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.

Primary Efficacy Outcome Data From Variable-Dose Pivotal Trials

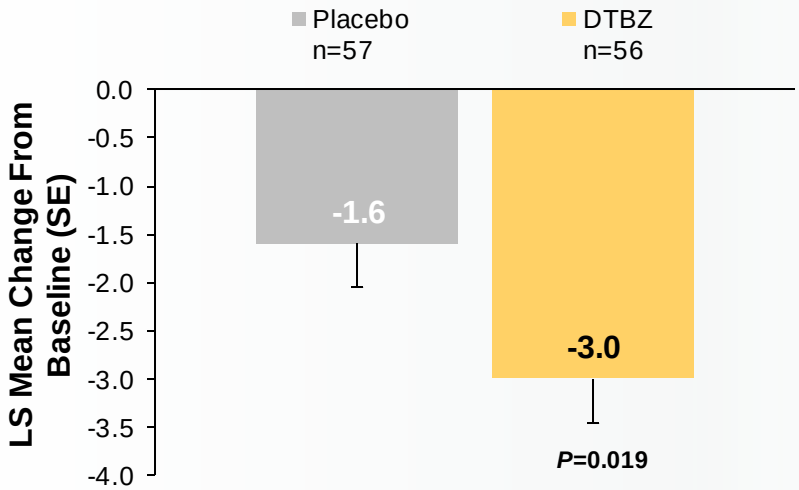
KINECT 2[1*]

AIMS Change From Baseline at **Week 6**
Primary Efficacy Endpoint



ARM-TD[2]

AIMS Change From Baseline at **Week 12**
Primary Efficacy Endpoint



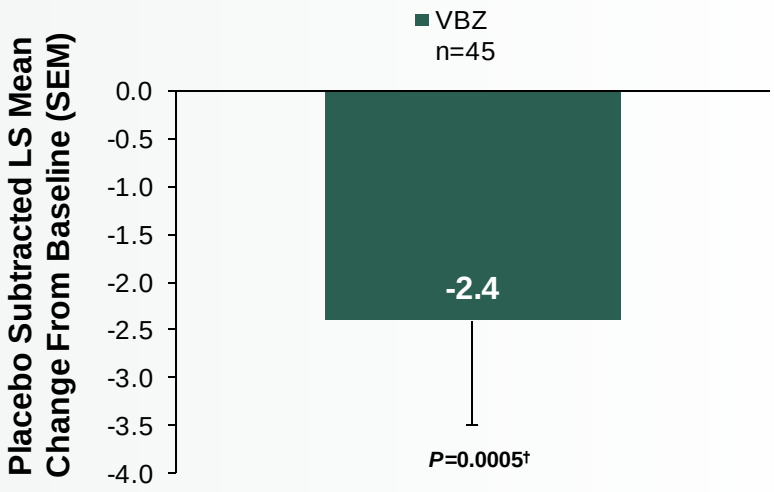
*ITT: Included all randomized participants who had at least one post-randomization AIMS value.
†*P* values are based on an ANCOVA at Week 6, using baseline value as a covariate and treatment and disease category as fixed effects.

References: 1. O'Brien CF et al. *Mov Disord.* 2015;30(12):1681-1687. 2. Fernandez HH et al. *Neurology.* 2017;88(21):2003-2010.

Placebo Subtracted Efficacy Outcome Data From Variable-Dose Pivotal Trials

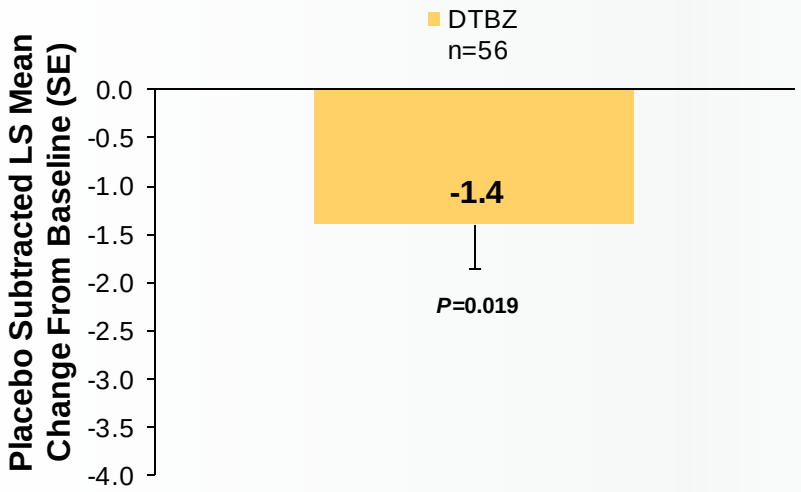
KINECT 2[1*]

AIMS Change From Baseline at **Week 6**
Primary Efficacy Endpoint



ARM-TD[2]

AIMS Change From Baseline at **Week 12**
Primary Efficacy Endpoint



*ITT: Included all randomized participants who had at least one post-randomization AIMS value.
†*P* values are based on an ANCOVA at Week 6, using baseline value as a covariate and treatment and disease category as fixed effects.

References: 1. O'Brien CF et al. *Mov Disord.* 2015;30(12):1681-1687. 2. Fernandez HH et al. *Neurology.* 2017;88(21):2003-2010.

ITC of Valbenazine and Deutetrabenazine: Results

Results of ITC Comparing Valbenazine and Deutetrabenazine

- Since the lowest dosage of 12 mg in the AIM-TD study did not demonstrate efficacy, a more conservative analysis was conducted that excluded the 12 mg dose from the pooled analysis
  - Removing data that skew favorability to valbenazine improves credibility
- Pooled data in the ITC of valbenazine and deutetrabenazine allow 4 pivotal trials into account, which provides a stronger analysis
  - These data present insights into overall populations because not all doses work for all patients

In the majority of comparisons, the results either favored valbenazine or were neutral

Reference: 1. Aggarwal S et al. *J Comp Eff Res.* 2019;8(13):1077-1088.

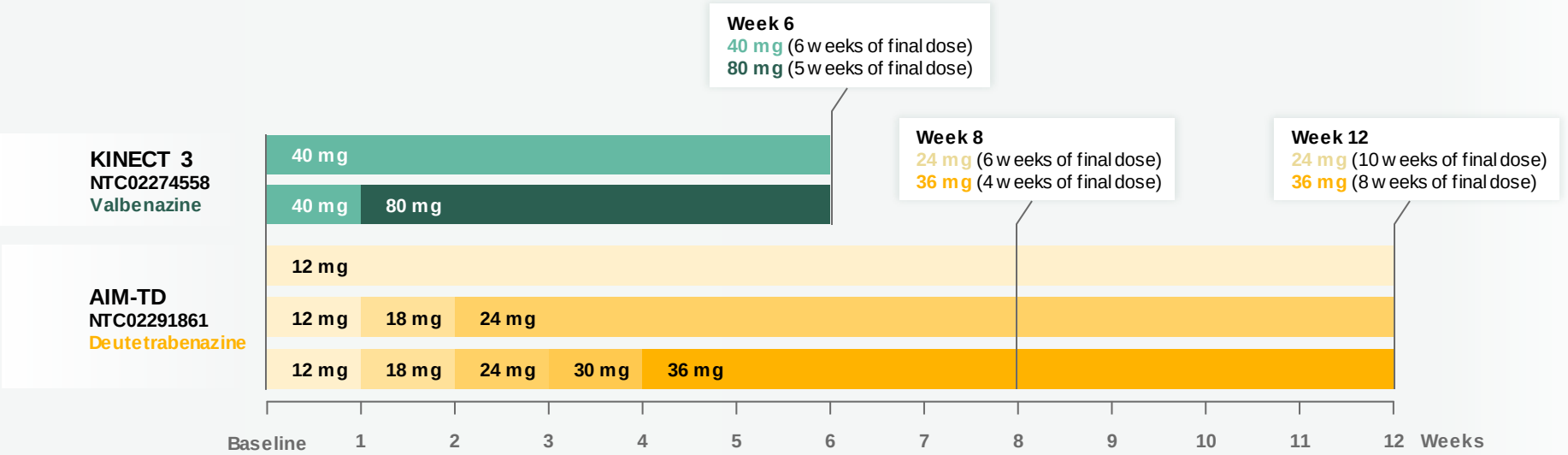
ITC of Valbenazine and Deutetrabenazine: Results by Dose

Indirect Treatment Comparison: Dose Comparison Methodology

Fixed dose studies were used to compare efficacy outcomes by dose (KINECT 3 and AIM-TD)

- Valbenazine (VBZ) 40 mg or 80 mg at Week 6
- Deutetrabenazine (DTBZ) 24 mg or 36 mg, Week 8 or Week 12

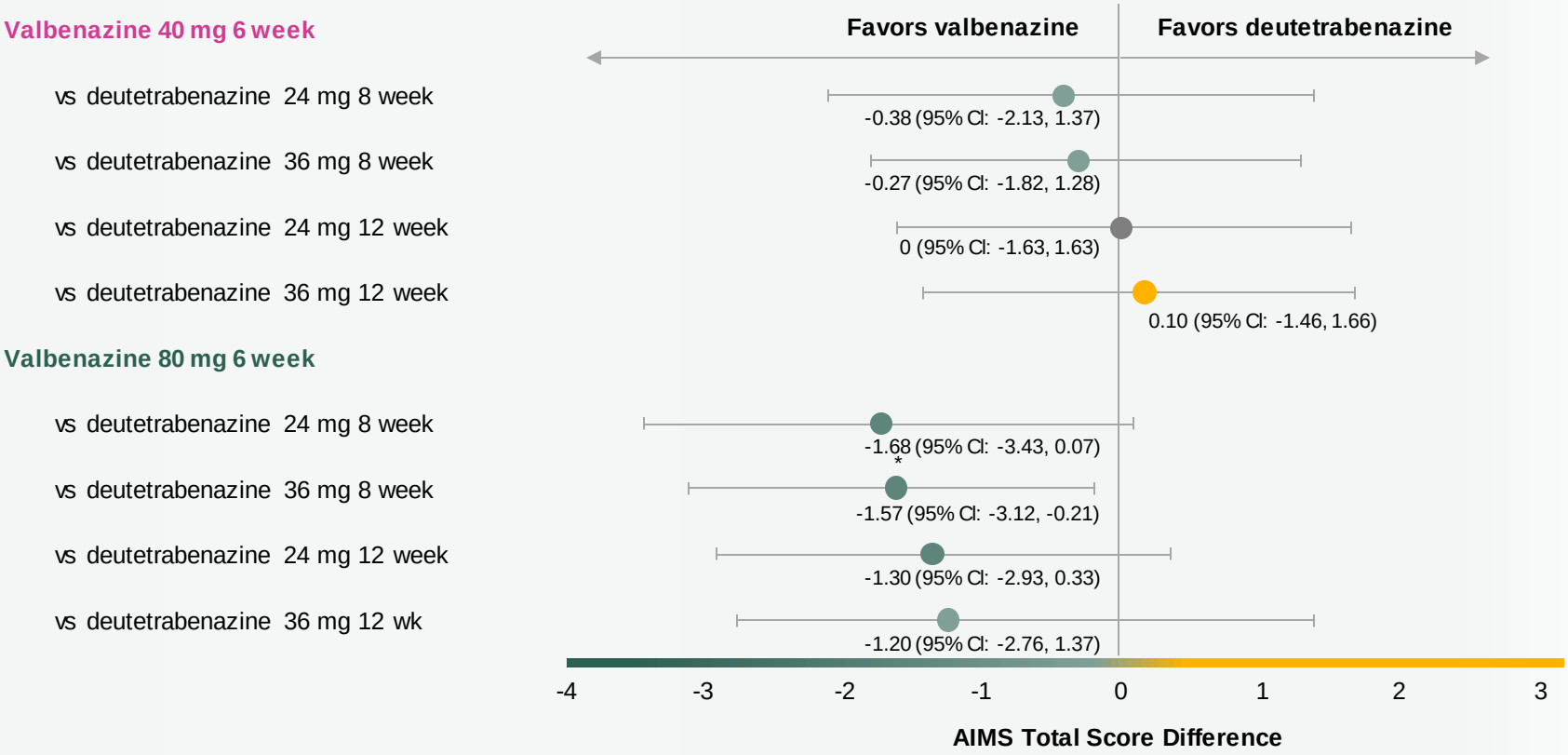
- Due to different dosing periods, comparable time points were analyzed from the studies
  - VBZ 6-week AIMS mean changes from baseline were compared to DTBZ Week 8 (AIM-TD) using a plot digitizer



Reference: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

ITC of Pivotal Trials: AIMS Change From Baseline by Dose

Mean Difference Between Valbenazine and Deutetrabenazine in AIMS CFB



**P*<0.05 for VBZ vs DTBZ.
CI=confidence interval.

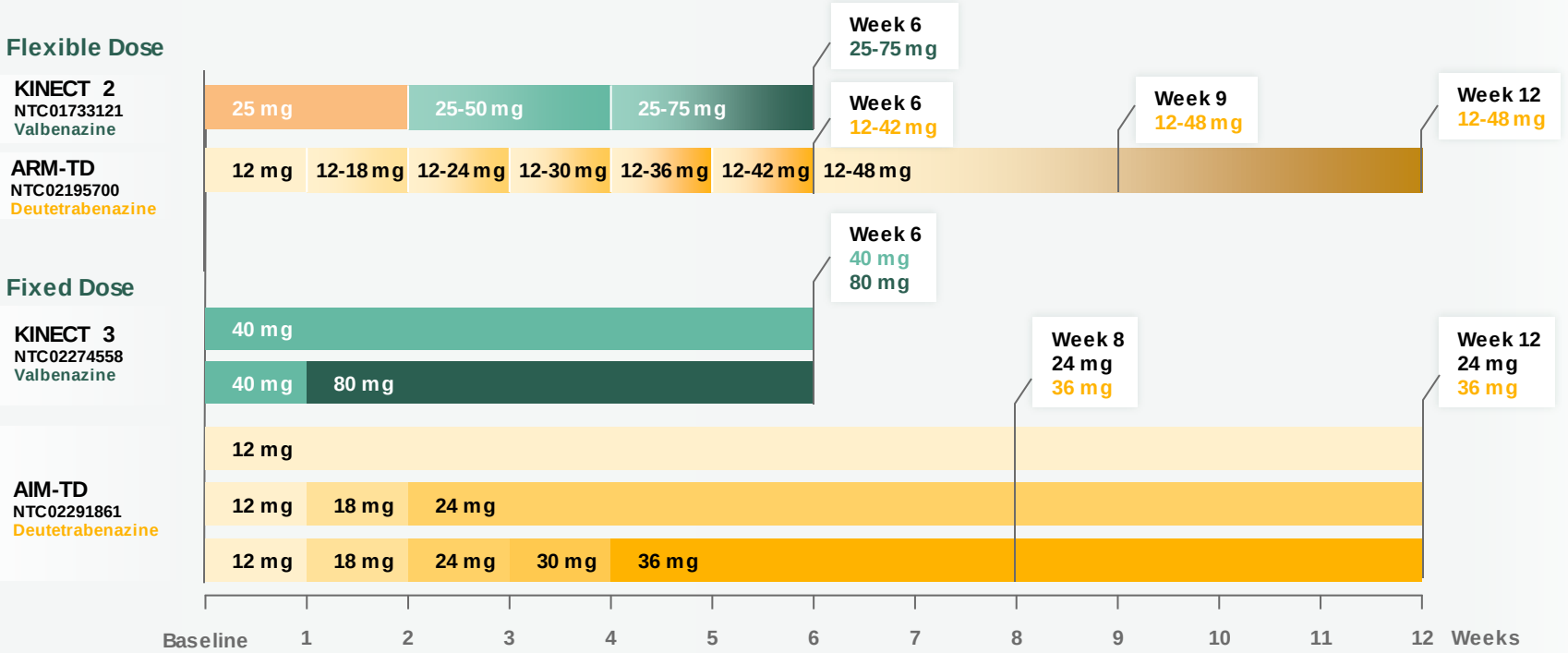
Reference: 1. Aggarwal S, et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

ITC of Valbenazine and Deutetrabenazine: Pooled Analyses Results

ITC of Pivotal Trials: Pooled Comparison From 4 RCTs

Valbenazine (VBZ) KINECT 2/3, 25 mg to 80 mg and Deutetrabenazine (DTBZ) AIM-TD/ARM-TD, 12 mg to 48 mg

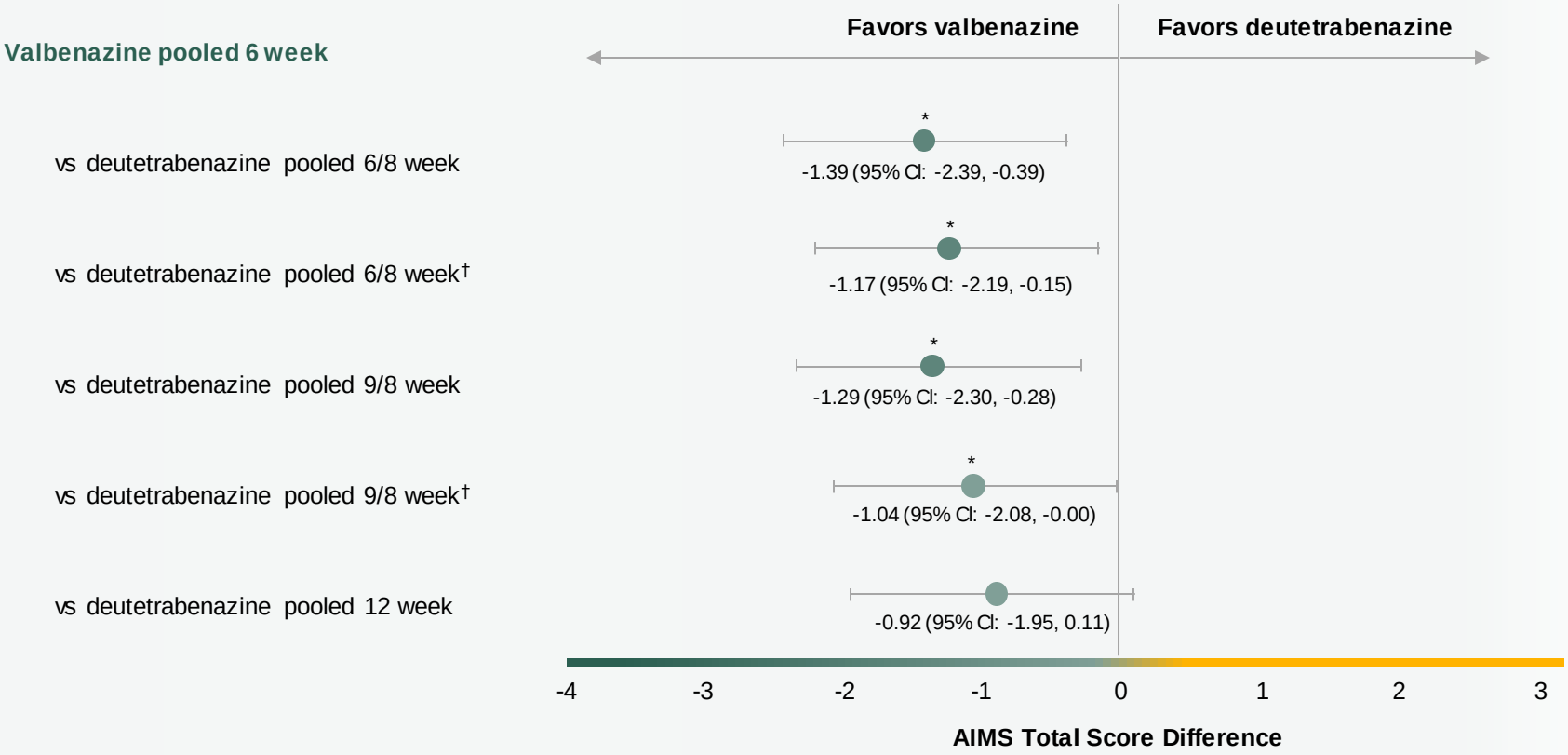
- Since efficacy was not demonstrated for the lowest dosage in AIM-TD (12 mg), a more conservative analysis was conducted in which this dose was excluded from the deutetrabenazine dataset
- Week 6 (VBZ) versus Weeks 6/8, 9/8, and Week 12 (DTBZ)
  - Due to different dosing, periods we analyzed comparable time points from the studies
  - VBZ 6-week AIMS mean changes from baseline were compared to DTBZ Weeks 6/8 (ARM-TD/AIM-TD) and Week 9/8 (ARM-TD/AIM-TD) using a plot digitizer



Reference: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

ITC of Pivotal Trials: Pooled Analyses
AIMS Change From Baseline by Timepoint

Mean Difference Between Pooled Valbenazine and Pooled Deutetrabenazine in AIMS CFB



**P*<0.05 for VBZ vs DTBZ.
†Without 12 mg arm.

Reference: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

ITC of Valbenazine and Deutetrabenazine: Secondary Efficacy Results

ITC of Pivotal Trials: Pooled Analyses—ORs and 95% CIs for AIMS Response Rates and CGIC Response Rates for VBZ (6 weeks) Versus DTBZ (12 weeks)

Valbenazine Group (n)	Deutetrabenazine Group (n)	OR (95% CI)
AIMS Response (≥50% total score improvement)		
Individual trial comparison		
KINECT 2 (45)	ARM-TD (48)	2.91 (0.74, 11.44)
KINECT 3 (133)	AIM-TD (164)	1.94 (0.55, 6.82)
Dosage comparison		
KINECT 3 40 mg (63)	AIM-TD 24 mg (49)	0.85 (0.21, 3.50)
KINECT 3 40 mg (63)	AIM-TD 36 mg (55)	0.93 (0.23, 3.79)
KINECT 3 80 mg (70)	AIM-TD 24 mg (49)	1.81 (0.46, 7.17)
KINECT 3 80 mg (70)	AIM-TD 36 mg (55)	1.98 (0.50, 7.77)
Pooled comparison		
KINECT 2/3 (178)	ARM-TD/AIM-TD (212)	2.30 (0.91, 5.81)
CGIC Response (score ≤2 at end point)		
Individual trial comparison		
KINECT 2 (45)	ARM-TD (48)	5.16 (1.4, 19.04)*
KINECT 3 (113)	AIM-TD (164)	1.14 (0.43, 3.03)
Dosage comparison		
KINECT 3 40 mg (52)	AIM-TD 24 mg (49)	0.79 (0.25, 2.51)
KINECT 3 40 mg (52)	AIM-TD 36 mg (55)	0.97 (0.31, 3.08)
KINECT 3 80 mg (61)	AIM-TD 24 mg (49)	0.78 (0.25, 2.44)
KINECT 3 80 mg (61)	AIM-TD 36 mg (55)	0.97 (0.31, 3.0)
Pooled comparison		
KINECT 2/3 (158)	ARM-TD/AIM-TD (212)	2.34 (0.45, 12.12)

*Statistical significance (*P*<0.05).
OR=odds ratio.

Reference: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

ITC of Valbenazine and Deutetrabenazine: Safety Results

ITC of Pivotal Trials: 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.

References: 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.

ITC of Pivotal Trials: Safety Results—KINECT 2 and ARM-TD Titration Trials

	KINECT 2[1]		ARM-TD[2]	
	PBO (n=49)	VBZ (n=51)	PBO (n=59)	dTBZ (n=58)
Serious TEAE, n	4	0	5	3
Treatment-emergent AE, (%)	32.7	49	61	70.7
Discontinuation/withdrawal due to TEAE, n	0	0	2	1
TEAE leading to dose reduction, n			3	6
TEAE leading to dose suspension, n			5	3

References: 1. O'Brien CF et al. *Mov Disord.* 2015;30(12):1681-1687. 2. Fernandez HH et al. *Neurology.* 2017;88(21):2003-2010.

ITC of Pivotal Trials: Safety Results—ORs and 95% CIs for TEAEs for VBZ (6 Weeks) Versus DTBZ (12 Weeks)

Valbenazine Group (n)	Deutetrabenazine Group (n[a])	OR (95% CI)
TEAEs		
Individual trial comparison		
KINECT 2 (51)	ARM-TD (58)	1.17 (0.35, 3.90)
KINECT 3 (151)	AIM-TD (221)	1.68 (0.68, 4.10)
Dosage comparison		
KINECT 3 40 mg (72)	AIM-TD 24 mg (73)	1.78 (0.56, 5.64)
KINECT 3 40 mg (72)	AIM-TD 36 mg (74)	0.98 (0.33, 2.88)
KINECT 3 80 mg (79)	AIM-TD 24 mg (73)	2.70 (0.86, 8.45)
KINECT 3 80 mg (79)	AIM-TD 36 mg (74)	1.49 (0.52, 4.31)
Pooled comparison		
KINECT 2/3 (202)	ARM-TD/AIM-TD (279)	1.78 (0.90, 3.51)
SAEs		
Individual trial comparison		
KINECT 2 (51)	ARM-TD (58)	NA*
KINECT 3 (151)	AIM-TD (221)	1.77 (0.68, 4.10)
Dosage comparison		
KINECT 3 40 mg (72)	AIM-TD 24 mg (73)	0.94 (0.08, 10.82)
KINECT 3 40 mg (72)	AIM-TD 36 mg (74)	1.47 (0.12, 18.95)
KINECT 3 80 mg (79)	AIM-TD 24 mg (73)	1.31 (0.13, 13.37)
KINECT 3 80 mg (79)	AIM-TD 36 mg (74)	2.06 (0.18, 23.53)
Pooled comparison		
KINECT 2/3 (202)	ARM-TD/AIM-TD (279)	0.88 (0.14, 5.56)

Valbenazine Group (n)	Deutetrabenazine Group (n[a])	OR (95% CI)
Discontinuations due to TEAEs		
Individual trial comparison		
KINECT 2 (51)	ARM-TD (58)	NA*
KINECT 3 (151)	AIM-TD (221)	0.77 (0.07, 8.52)
Dosage comparison		
KINECT 3 40 mg (72)	AIM-TD 24 mg (73)	1.07 (0.05, 25.31)
KINECT 3 40 mg (72)	AIM-TD 36 mg (74)	0.72 (0.04, 13.23)
KINECT 3 80 mg (79)	AIM-TD 24 mg (73)	1.23 (0.06, 27.52)
KINECT 3 80 mg (79)	AIM-TD 36 mg (74)	0.82 (0.05, 14.32)
Pooled comparison		
KINECT 2/3 (202)	ARM-TD/AIM-TD (279)	1.20 (0.17, 8.59)

*Indirect treatment comparisons were not feasible because there were no discontinuations due to TEAEs and SAEs in KINECT 2.
NA=not applicable; SAEs=serious adverse events.

Reference: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

ITC of Valbenazine and Deutetrabenazine: Limitations

ITC of Pivotal Trials: Limitations

- As noted by Bucher,[1] the strength of inference from indirect comparisons is limited[2]
- Inter-trial variability in baseline populations, treatment duration, and titration schedules can affect results. However baseline characteristics were similar among trials[2]
- To account for the potential differences in treatment durations and titration schedules in the ITC analysis, multiple comparisons were conducted at different time points[2]

References: 1. Bucher HC et al. *J Clin Epidemiol*.1997;50:683-691. 2. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

ITC of Valbenazine and Deutetrabenazine: Conclusion

ITC of Pivotal Trials: Summary of Efficacy and Safety Results

Endpoint		Statistically Significant VBZ	Favors VBZ*	Neutral†	Favors DTBZ*	Statistically Significant DTBZ
AIMS CFB 40 mg VBZ (6 weeks)	24 mg DTBZ (8 weeks)					
	36 mg DTBZ (8 weeks)					
AIMS CFB 80 mg VBZ (6 weeks)	24 mg DTBZ (8 weeks)					
	36 mg DTBZ (8 weeks)					
AIMS CFB Pooled at 6 weeks	Pooled DTBZ (6/8 or 9/8 weeks)					
	Pooled DTBZ (12 weeks)					
50% AIMS Response VBZ 6 weeks	DTBZ 12 weeks					
CGIC Response VBZ 6 weeks	DTBZ 12 weeks					
Safety	TEAE					
	SAE					
	Discontinuation due to TEAE					

*OR point estimate >1.5, AIMS CFB point estimate difference >0.5.
†OR point estimate <1.5, AIMS CFB point estimate difference <0.5.

Reference: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

Summary of Efficacy Results

- VBZ 80 mg at 6 weeks showed favorable efficacy compared to DTBZ 36 mg or 24 mg at 8 weeks
- VBZ 40 mg at 6 weeks showed similar efficacy compared to DTBZ 36 mg or 24 mg at 8 weeks
  - At 6 weeks, AIMS CFB by dosage ITC for VBZ 40 mg was similar to DTBZ 24 mg and 36 mg at 8 weeks
  - VBZ 80 mg at 6 weeks was favored with statistical significance ($P<0.05$) compared to DTBZ 36 mg at 8 weeks
- In the ITC of pooled studies, VBZ displayed statistically significant reductions in AIMS CFB ($P<0.05$) at 6 weeks compared to DTBZ at 6/8 weeks or 9/8 weeks
- There were no significant differences in individual trial and pooled comparisons of AIMS and CGIC responses
- VBZ showed a statistically favorable efficacy in AIMS reduction from baseline at ~6 weeks compared to DTBZ in pooled analyses over similar time frames
  - VBZ trends toward favorable efficacy measured by AIMS reduction from baseline, AIMS ≥50% response, and CGIC response when 12-week DTBZ data were used in the ITC
- Methodology and other study factors such as inclusion criteria, concomitant medications, and TD severity may need to be considered when interpreting the results

Reference: 1. Aggarwal S et al. *J Comp Eff Res.* 2019;8(13):1077-1088.

Summary of Safety and Study Limitations

- The ITC of pooled studies indicated no significant differences in any safety outcome analyzed
  - Deutetrabenazine displayed a trend toward favorable safety for TEAEs but not SAEs
- Safety outcomes were assessed over different time courses for valbenazine (6-week) and deutetrabenazine (12-week) trials; however, all indirect comparisons are placebo adjusted
- Methodology and other study factors such as inclusion criteria, concomitant medications, and tardive dyskinesia severity may need to be considered when interpreting the results

Reference: 1. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

Backup

Backup

ITC and Network Meta-Analysis (NMA)

Indirect Treatment Comparison: Identify Relevant Studies

- All RCT data must be found during a literature search and populations must be homogeneous to aggregate[1,2]

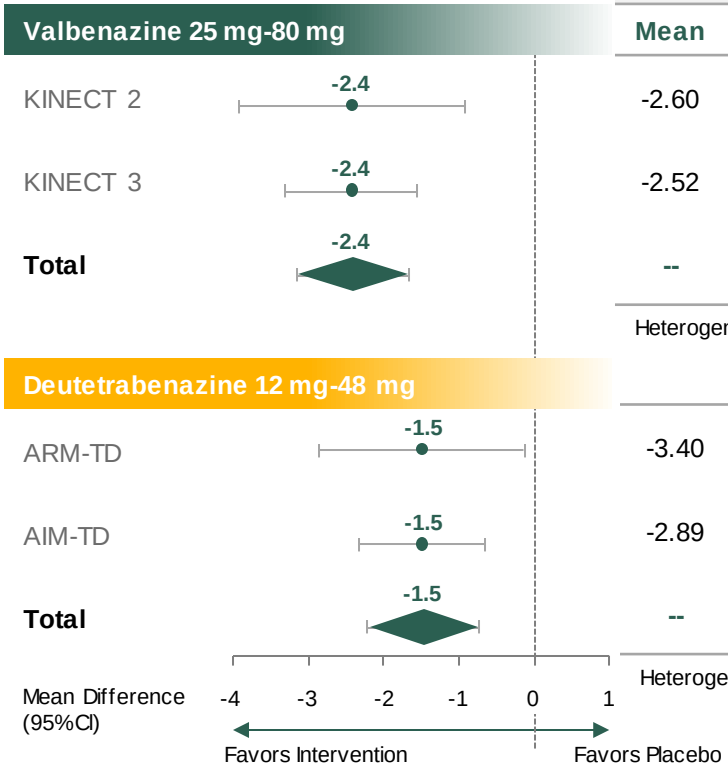
Study Name (Trial ID)	Study Design (Duration)	Study Drug (Doses)	Key Eligibility Criteria
KINECT 2[3] (NCT01733121)	RDBPC (6 weeks)	Valbenazine (25 mg-75 mg; QD)	• Drug-induced TD for ≥3 months • Moderate or severe TD at screening (per judgment of independent rater) • Stable psychiatric status • Stable doses of psychiatric medications allowed • Concomitant anticholinergics allowed
KINECT 3[4] (NCT02274558)	RDBPC (6 weeks)	Valbenazine (40 mg or 80 mg; QD)	• Drug-induced TD for ≥3 months • Moderate or severe TD at screening (per judgment of independent rater) • Stable psychiatric status • Stable doses of psychiatric medications allowed • Concomitant anticholinergics allowed
ARM-TD[5] (NCT02195700)	RDBPC (12 weeks)	Deutetrabenazine (12 mg-48 mg; 6 mg-24 mg BID)	• Drug-induced TD for ≥3 months • AIMS total score ≥6 at screening and baseline (confirmed by blinded central rater) • Stable psychiatric status • Stable doses of psychiatric medications allowed • Strong anticholinergics not allowed
AIM-TD[6] (NCT02291861)	RDBPC (12 weeks)	Deutetrabenazine (12 mg, 24 mg, or 36 mg; 6 mg, 12 mg, or 18 mg BID)	• Drug-induced TD for ≥3 months • AIMS total score ≥6 at screening and baseline (confirmed by blinded central rater) • Stable psychiatric status • Stable doses of psychiatric medications allowed • Strong anticholinergics not allowed

BID=twice-daily (divided doses); QD=once-daily; RDBPC=randomized double-blind placebo-controlled; TD=tardive dyskinesia.

References: 1. Aggarwal S et al. Poster presented at: AMCP NEXUS 2018; October 22-25, 2018. Orlando, FL. 2. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088. 3. O'Brien CF et al. *Mov Disord*. 2015;30:1681-1687. 4. Hauser RA, et al. *Am J Psychiatry*, 2017;174(5):476-484. 5. Fernandez et al. *Neurology*. 2017;88:1-8. 6. Anderson KE et al. *Lancet Psychiatry*. 2017;4(8):595-604.

Indirect Treatment Comparison: Conduct Meta-Analysis

- Meta-analysis results: AIMS mean score change from baseline (all doses)[1,2]
  - Results from the 4 included studies and how they individually compare treatment to placebo



	Intervention			Placebo				
	Mean	SD	Total	Mean	SD	Total	Weight	MD (95% CI)
KINECT 2	-2.60	3.50	45	-0.2	3.7	44	25.5	-2.40 (-3.90,-0.90)
KINECT 3	-2.52	2.30	133	-0.1	3.32	69	74.5	-2.42 (-3.30,-1.54)
Total	--	--	**178**	--	--	**113**	**100.0**	**-2.41 (-3.17,-1.66)**

Heterogeneity: Tau^2=0.00; Chi^2=0.00; df=1 (*P*=0.98); I^2=0%; Test for overall effect" Z=6.26 (*P*<0.001)

ARM-TD	-3.40	3.33	48	-1.9	3.57	49	27.7	-1.50 (-2.87,-0.13)
AIM-TD	-2.89	1.83	164	-1.4	3.12	58	72.3	-1.49 (-2.34,-0.64)
Total	--	--	**212**	--	--	**107**	**100.0**	**-1.49 (-2.22,-0.77)**

Heterogeneity: Tau^2=0.00; Chi^2=0.00; df=1 (*P*=0.99); I^2=0%; Test for overall effect" Z=4.05 (*P*<0.001)

df=degrees of freedom; MD=mean difference.

References: 1. Aggarwal S et al. Poster presented at: AMCP NEXUS 2018; October 22-25, 2018. Orlando, FL. 2. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.

Indirect Treatment Comparison: ISPOR Checklist of Good Research Practices for Conducting and Reporting Network Meta-Analysis Studies

Checklist Item	Recommendation(s)
Search	• Follow conventional guidelines for systematic literature searches; be explicit about search terms, literature, and time frames, and avoid use of ad hoc data • Consider iterative search methods to identify higher-order indirect comparisons that do not come up in the initial search, focusing on lower-order indirect comparisons
Data collection	• Set forth evidence network demonstrating direct and indirect linkages between treatments, based on identified study reports • Follow conventional guidelines for data collection; use a prespecified protocol and data extraction form • Include sufficient study detail in data extraction to permit assessment of comparability and homogeneity (eg, patient and study characteristics, comparators, and outcome measures)
Statistical analysis plan	• Prepare statistical analysis plan prior to data analysis, but permit modifications during data analysis, if necessary • Provide step-by-step descriptions of all analyses, including explicit statements of all assumptions and procedures for checking them • Describe analytic features specific to network meta-analysis, including comparability and homogeneity, synthesis, sensitivity analysis, subgroup analysis and meta-regression, and special types of outcomes
Data analysis	• Follow conventional guidelines for statistical model diagnostics • Evaluate violations of similarity or consistency assumption in evidence network • If similarity or consistency is a problem, consider use of meta-regression models with treatment covariate interactions to reduce bias
Reporting	• Follow PRISMA statement for reporting of meta-analysis • Explicitly state the study research questions (eg, in Introduction or Objectives section of report) • Provide graphical depiction of evidence network • Indicate software package used in the analysis and provide code (at least in an online appendix)

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

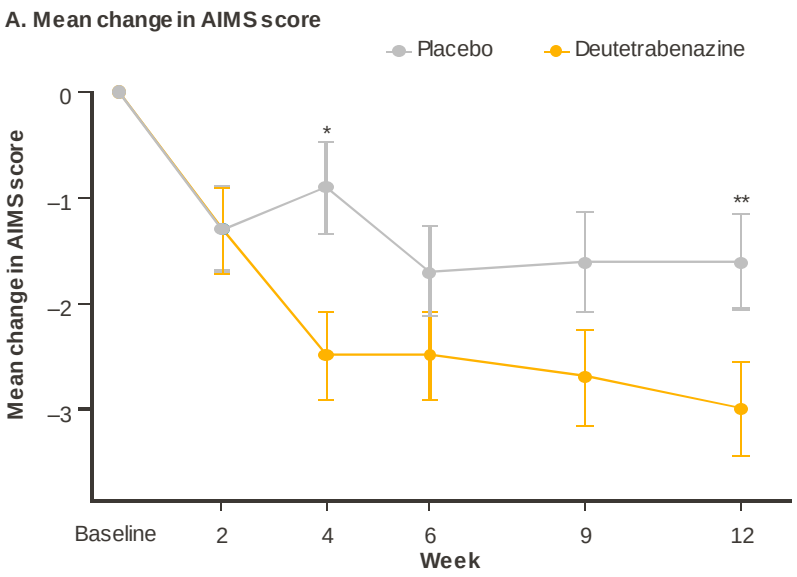
Reference: 1. Hoaglin DC et al. *Value Health.* 2011;14(4):429-437.

Backup

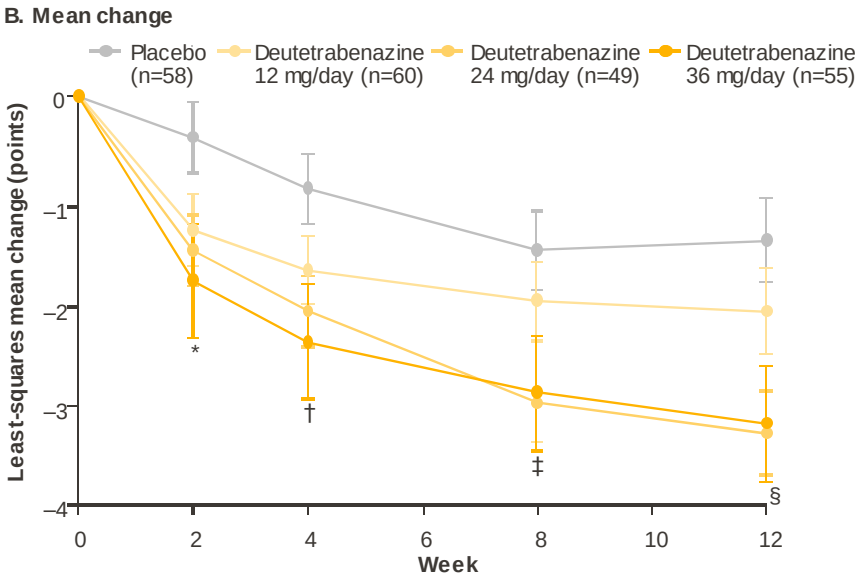
ITC of Valbenazine and Deutetrabenazine: Additional Results and RCT Data

Indirect Treatment Comparison—Pivotal Trial Results: Digitizing Graphs

ARM-TD



AIM-TD



- Published data, including RCT data, is often presented only in a figure[1]
- For use in a comparison, it must be extracted into a numerical format[1,2]
- Plot digitization is a software program to conduct this process[1,2]

References: 1. Puljak L. https://training.cochrane.org/sites/training.cochrane.org/files/public/uploads/resources/downloadable_resources/2016_11_webinar_Puljak-extracting-data-from-figures.pdf. Accessed August 21, 2020. 2. Aggarwal S et al. *J Comp Eff Res*. 2019;8(13):1077-1088.