Comparison of Safety and Tolerability of Deutetrabenazine During Titration and Maintenance in Patients With Tardive Dyskinesia

Amanda Wilhelm, PhD[1]; Karen E. Anderson, MD[2]; Hubert H. Fernandez, MD[3]; Hadas Barkay, PhD[4]; Nayla Chaijale, PhD[1]; Alexander F. Send, PhD[1]; Juha-Matti Savola, MD, PhD[5]; Mark Forrest Gordon, MD[1]

[1]Teva Pharmaceuticals, West Chester, PA, USA; [2]Georgetown University, Washington, DC, USA; [3]Cleveland Clinic, Cleveland, OH, USA; [4]Teva Pharmaceuticals, Netanya, Israel; [5]Teva Pharmaceuticals, Basel, Switzerland.

Conclusions

- Overall, deutetrabenazine was generally well tolerated in patients with tardive dyskinesia (TD), with adverse event (AE) rates similar to placebo during both the titration and maintenance periods
- Patients with TD treated with deutetrabenazine experienced higher rates of AEs during titration and lower rates during maintenance
- These findings provide important context for the dosing schedule to providers and patients

Background

- Exposure to dopamine-receptor antagonists (DRAs) may cause TD, a potentially debilitating involuntary movement disorder[1,2]
- The novel vesicular monoamine transporter 2 (VMAT2) inhibitor deutetrabenazine is approved by the US Food and Drug Administration for treatment of TD and chorea associated with Huntington's disease in adults[3]
- In two pivotal, 12-week, placebo-controlled, phase 3 studies (ARM-TD and AIM-TD), deutetrabenazine demonstrated significant improvements in Abnormal Involuntary Movement Scale (AIMS) score, with favorable safety and tolerability and low rates of discontinuation[4,5]; in an open-label extension (OLE) of these studies, long-term deutetrabenazine treatment was well tolerated and efficacious in patients with TD[6]

Objective

- To compare the safety of deutetrabenazine during the titration versus maintenance periods

Methods

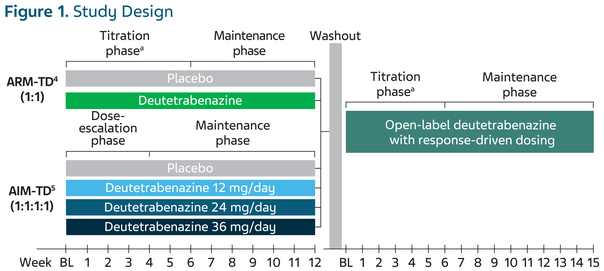
Study Design

- ARM-TD and AIM-TD were 12-week, randomized, placebo-controlled trials of deutetrabenazine in patients with TD.[4,5] The OLE study was a 3-year, single-arm trial that enrolled patients who completed ARM-TD or AIM-TD[6] (**Figure 1**)
  - ARM-TD randomized (1:1) patients to receive either deutetrabenazine or placebo to evaluate the efficacy and safety of deutetrabenazine in patients with TD[4]
  - AIM-TD randomized (1:1:1:1) patients to receive either placebo or fixed-dose deutetrabenazine (12 mg/day, 24 mg/day, or 36 mg/day) to evaluate the efficacy, safety, and tolerability of deutetrabenazine in patients with TD[5]
  - The OLE study was a single-arm trial that enrolled patients who completed ARM-TD or AIM-TD and evaluated long-term efficacy and safety of deutetrabenazine following a response-driven dosing regimen similar to ARM-TD

Analyses

- Safety was assessed during the titration versus maintenance periods using integrated data from ARM-TD, AIM-TD, and through Week 15 of the OLE study
  - Data from the placebo groups in ARM-TD and AIM-TD were pooled for this analysis
  - The flexible-dose deutetrabenazine group pooled data from patients who received deutetrabenazine during ARM-TD and data from the OLE study
- Rates were compared for overall AEs, serious AEs, AEs leading to discontinuation, treatment-related AEs, common AEs, and specific AEs
  - Common AEs were defined as those occurring in ≥4% of patients
  - Specific AEs included parkinsonism, suicidal ideation, akathisia, and restlessness

Figure 1. Study Design



BL, baseline; AE, adverse event.
[a]Titration occurred until (i) adequate dyskinesia control was achieved, (ii) a clinically significant AE occurred, or (iii) a maximum dose of 48 mg/day was reached (36 mg/day for patients receiving a strong CYP2D6 inhibitor).
ARM-TD: Titration: From the first dose of treatment until the time point before the first dose of study drug received at the Week 6 visit (up to 48 mg/day); Maintenance: From the first dose time point of treatment received at the Week 6 visit until the Week 12 visit.
AIM-TD: Dose escalation: From the first dose of treatment until the day before the Week 5 telephone contact or until randomized dose was achieved; Maintenance: From the day of the Week 5 telephone contact until the day of the Week 12 visit.
OLE: Titration: From the first dose of treatment until 7 days after the Week 6 visit (up to 48 mg/day); Maintenance (for this analysis): From 8 days after the Week 6 visit until the day of the Week 15 visit.

Results

Patients

- Baseline characteristics were generally similar across treatment groups in the integrated analysis (**Table 1**)

Table 1. Baseline Characteristics[a]

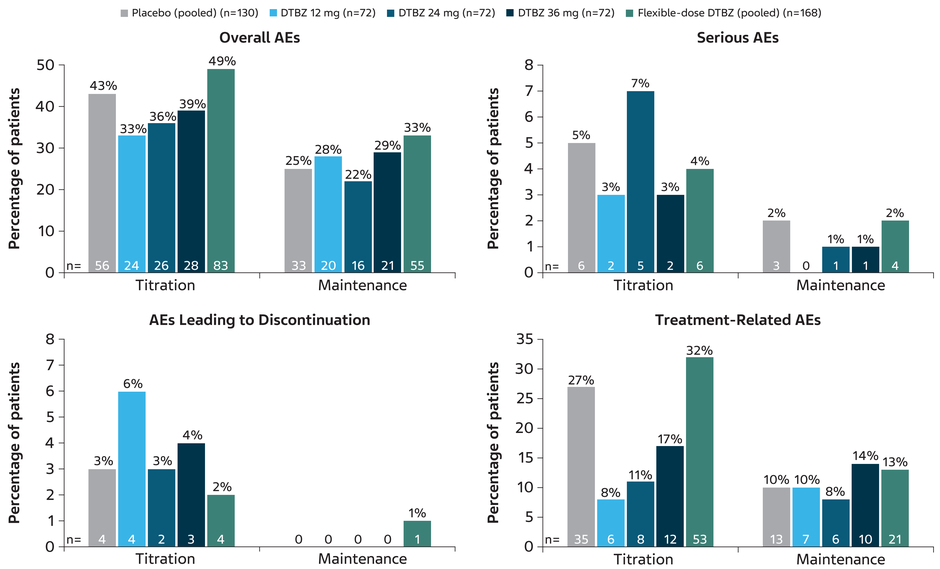
	Placebo (pooled) (n=130)	DTBZ 12 mg (n=72)	DTBZ 24 mg (n=72)	DTBZ 36 mg (n=72)	Flexible-dose DTBZ (pooled) (n=168)
Patient demographics					
Age (years), mean (SD)	54.3 (11.2)	57.2 (9.9)	55.8 (11.4)	58.6 (11.5)	55.3 (10.9)
Sex, female, n (%)	69 (53)	41 (57)	40 (56)	41 (57)	90 (54)
Race, white, n (%)	102 (78)	56 (78)	53 (74)	59 (82)	124 (74)
Patient clinical characteristics					
Total motor AIMS score, mean (SD)	9.0 (3.5)	8.6 (3.1)	7.7 (3.5)	8.5 (3.8)	9.1 (3.8)
TD duration (years), mean (SD)	6.2 (6.1)	5.5 (5.4)	5.0 (6.1)	6.0 (5.4)	6.1 (6.0)
Receiving DRA at baseline, n (%)	105 (81)	55 (76)	56 (78)	53 (74)	131 (78)
Background comorbid illness					
Psychotic disorders,[b] n (%)	83 (64)	40 (56)	49 (68)	44 (61)	107 (64)
Mood disorders,[c] n (%)	43 (33)	30 (42)	17 (24)	26 (36)	53 (32)
Other or missing, n (%)	4 (3)	2 (3)	6 (8)	2 (3)	8 (5)

DTBZ, deutetrabenazine; SD, standard deviation; AIMS, Abnormal Involuntary Movement Scale; TD, tardive dyskinesia; DRA, dopamine-receptor antagonist.
[a]Baseline characteristics were recorded at the start of each pivotal study; baseline total motor AIMS score was based on central reading.
[b]Schizophrenia, schizoaffective disorder.
[c]Bipolar disorder, depression.

Safety

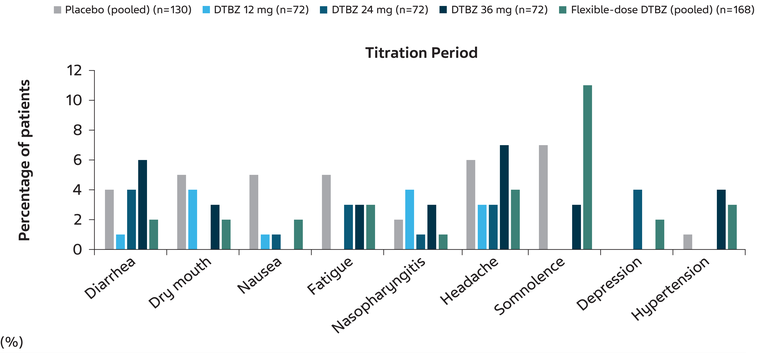
- Rates of overall AEs, serious AEs, AEs leading to discontinuation of study drug, and treatment-related AEs were generally higher during the titration period compared with the maintenance period (**Figure 2**)
- Common AEs (≥4%) during the titration period were diarrhea, dry mouth, nausea, fatigue, nasopharyngitis, headache, somnolence, depression, and hypertension; only 1 AE (headache) met this threshold during the maintenance period (**Figure 3**)
- Rates of specific AEs were low and comparable during the titration and maintenance periods (**Table 2**)

Figure 2. AEs in the Titration Versus Maintenance Periods



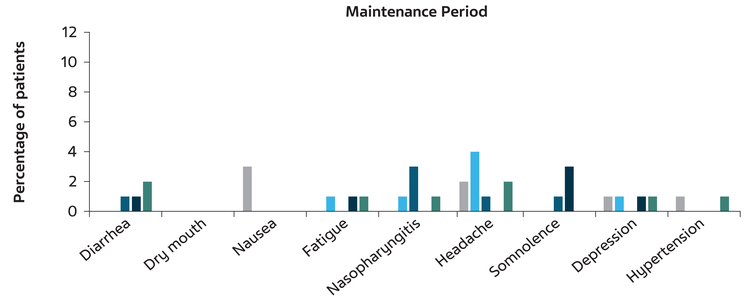
AE, adverse event; DTBZ, deutetrabenazine.

Figure 3. Common AEs (≥4%) in the Titration Versus Maintenance Periods



n (%)

	Diarrhea	Dry mouth	Nausea	Fatigue	Nasopharyngitis	Headache	Somnolence	Depression	Hypertension
Placebo (pooled)	5 (4)	6 (5)	7 (5)	6 (5)	2 (2)	8 (6)	9 (7)	0	1 (1)
DTBZ 12 mg	1 (1)	3 (4)	1 (1)	0	3 (4)	2 (3)	0	0	0
DTBZ 24 mg	3 (4)	0	1 (1)	2 (3)	1 (1)	2 (3)	0	3 (4)	0
DTBZ 36 mg	4 (6)	2 (3)	0	2 (3)	2 (3)	5 (7)	2 (3)	0	3 (4)
Flexible-dose DTBZ (pooled)	3 (2)	3 (2)	4 (2)	5 (3)	1 (1)	6 (4)	19 (11)	3 (2)	5 (3)



n (%)

	Diarrhea	Dry mouth	Nausea	Fatigue	Nasopharyngitis	Headache	Somnolence	Depression	Hypertension
Placebo (pooled)	0	0	4 (3)	0	0	2 (2)	0	1 (1)	1 (1)
DTBZ 12 mg	0	0	0	1 (1)	1 (1)	3 (4)	0	1 (1)	0
DTBZ 24 mg	1 (1)	0	0	0	2 (3)	1 (1)	1 (1)	0	0
DTBZ 36 mg	1 (1)	0	0	1 (1)	0	0	2 (3)	1 (1)	0
Flexible-dose DTBZ (pooled)	4 (2)	0	0	2 (1)	2 (1)	3 (2)	0	2 (1)	2 (1)

AE, adverse event; DTBZ, deutetrabenazine.

Table 2. Specific AEs in the Titration Versus Maintenance Periods

	Titration					Maintenance				
AE, n (%)	Placebo (pooled) (n=130)	DTBZ 12 mg (n=72)	DTBZ 24 mg (n=72)	DTBZ 36 mg (n=72)	Flexible-dose DTBZ (pooled) (n=168)	Placebo (pooled) (n=130)	DTBZ 12 mg (n=72)	DTBZ 24 mg (n=72)	DTBZ 36 mg (n=72)	Flexible-dose DTBZ (pooled) (n=168)
Parkinsonism	0	0	0	1 (1)	0	0	0	0	1 (1)	0
Suicidal ideation	0	0	2 (3)	0	0	1 (1)	0	0	1 (1)	0
Akathisia	0	0	0	0	1 (1)	0	0	1 (1)	0	3 (2)
Restlessness	0	1 (1)	0	0	0	0	0	0	0	0

AE, adverse event; DTBZ, deutetrabenazine.

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Disclosures: Amanda Wilhelm: Employee of Teva Pharmaceuticals. Karen E. Anderson: Scientific advisor: North American study co-principal investigator for LEGATO-HD, global principal investigator for AIM-TD, and global co-principal investigator for ARM-TD. Site principal investigator for Pride-HD, First-HD, ARC-HD: Teva. Scientific advisor, site principal investigator for ENROLL-HD: CHDI Foundation. Scientific advisor: Prana. Site principal investigator: Vaccinex. Consultant to the NeuroNext 105 study: Azevan. Salary support: The Griffin Foundation. She has also received honoraria from Vindico Medical Education. Hubert H. Fernandez: Honoraria: Prime Education, Inc., International Parkinson and Movement Disorders Society, Carling Communications, Medscape (speaker in CME events), AbbVie, Biogen, GE Health Care, Inventiv, Kyowa Hakko Kirin, Lundbeck, Merz Pharmaceuticals, Voyager, Sunovion, and Pfizer Pharmaceuticals (as a consultant). Grant and research support: AbbVie, Acadia, Teva, Biotie/Acorda Therapeutics, Civitas, Kyowa/Prostrakan, Michael J. Fox Foundation, Movement Disorders Society, NIH/NINDS, Parkinson Study Group, Rhythm, and Synosia. Dr. Fernandez has no owner interest in any pharmaceutical company. Royalties: Demos Publishing (serving as a book author/editor). Contractual services: The Cleveland Clinic has a contract with Teva for Dr. Fernandez's role as a co-principal investigator in deutetrabenazine tardive dyskinesia global studies. Dr. Fernandez also serves as a member of the publication committee for Acorda Pharmaceuticals but does not receive any personal compensation for this. Stipend: International Parkinson and Movement Disorders Society for serving as medical editor of the MDS website. Hadas Barkay: Employee of Teva Pharmaceuticals. Nayla Chaijale: Employee of Teva Pharmaceuticals. Alexander F. Send: Employee of Teva Pharmaceuticals. Juha-Matti Savola: Former employee of Teva Pharmaceuticals. Mark Forrest Gordon: Employee of Teva Pharmaceuticals.

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Email questions to Amanda.Wilhelm@tevapharm.com.