An Evaluation of Anticholinergic Adverse Events with Long-Term Use of Topical Glycopyrronium Tosylate, a Treatment for Primary Axillary Hyperhidrosis

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INTRODUCTION

- Hyperhidrosis, a chronic condition characterized by sweat production exceeding that which is necessary to maintain normal thermal homeostasis, has an estimated US prevalence of 4.8% (~15.3 million people)[1]
- Glycopyrronium tosylate (GT) is a topical anticholinergic recently approved by the US Food and Drug Administration for treatment of primary axillary hyperhidrosis in patients ≥9 years of age (glycopyrronium cloth, 2.4%, for topical use)[2]
- The efficacy and safety of GT were established in two double-blind, vehicle (VEH)-controlled phase 3 trials (ATMOS-1 [NCT02530281], ATMOS-2 [NCT02530294])[2,3]
- Long-term safety and tolerability of GT were evaluated in an open-label extension (ARIDO [NCT02553798]) of the two double-blind trials

OBJECTIVE

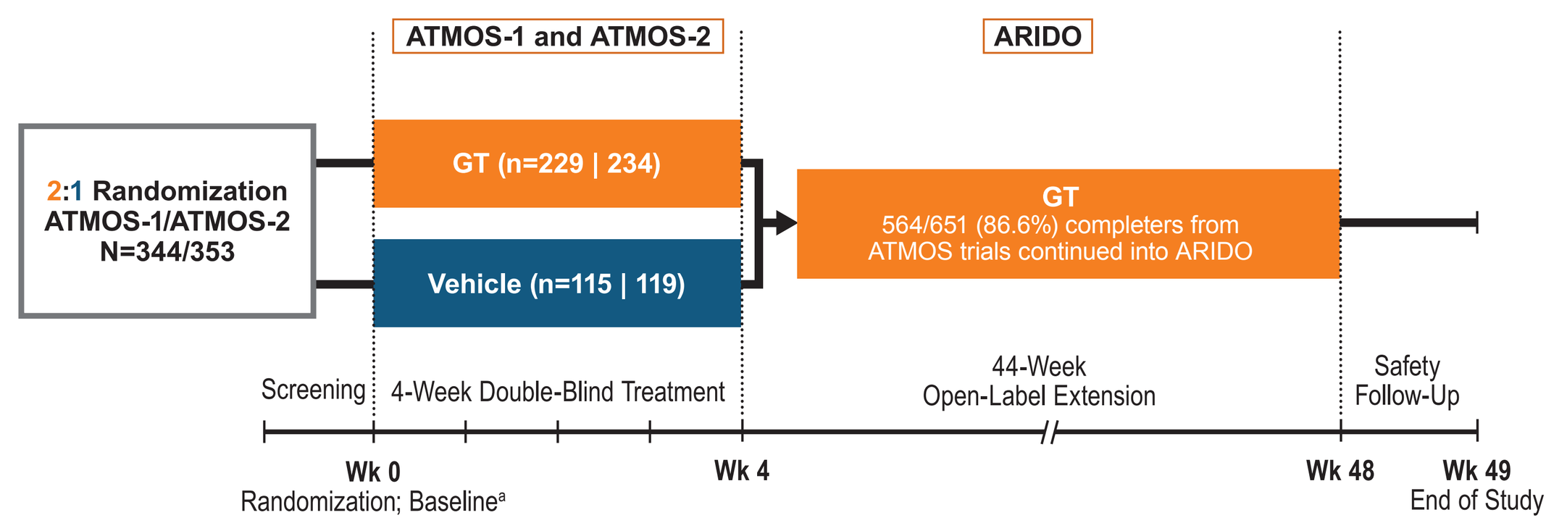
To evaluate the timing of treatment-emergent and anticholinergic adverse events and the management of anticholinergic adverse events during the open-label extension trial of GT

METHODS

Study Design

- Patients 9 years of age and older with primary axillary hyperhidrosis were randomized 2:1 to GT or VEH once-daily for 4 weeks in one of two parallel phase 3 trials: ATMOS-1 (sites in US and Germany) or ATMOS-2 (sites in US only; **Figure 1**)
- Patients completing Week 4 of the double-blind trials with 80% or higher compliance were given the option to receive GT in an open-label extension for up to an additional 44 weeks (**Figure 1**)
- Eligible patients were ≥9 years of age, had primary axillary hyperhidrosis for ≥6 months, gravimetrically measured sweat production of ≥50 mg/5 min in each axilla, Axillary Sweating Daily Diary (ASDD)/ASDD-Children (ASDD-C) Item 2 (severity) score ≥4 (0 to 10 numeric rating scale), and Hyperhidrosis Disease Severity Scale (HDSS) grade ≥3
- Patients were excluded for history of a condition that could cause secondary hyperhidrosis or that could be exacerbated by trial medication, prior surgical procedure for hyperhidrosis, prior axillary treatment with an anti-hyperhidrosis medical device within 4 weeks of Baseline, botulinum toxin within 1 year of Baseline, or use of other treatments with anticholinergic activity within 4 weeks of Baseline unless dosing was stable for ≥4 months prior to Baseline
- The open-label extension was terminated early per protocol upon at least 100 patients receiving GT for a total of 12 months, including the 4-week treatment in the double-blind trials

Figure 1. Study Design



[a]For efficacy assessments, Baseline for the ARIDO open-label extension was Week 0 of the double-blind ATMOS-1/ATMOS-2 trials
GT, Glycopyrronium tosylate; Wk, Week

Assessments

- Treatment-emergent adverse events (TEAEs) were recorded throughout the study
  - Patients were asked about adverse events in a non-specific manner using open-ended questions; specific inquiry and evaluation regarding reported adverse events were to be conducted when applicable
  - The duration of adverse events could be self-reported by patients but also could be noted as part of a symptom directed physical exam
- Patients were assessed in clinics at Day 1 (Week 4 of the double-blind trials) and Weeks 2, 4, 8, 12, 16, 20, 28, 36, and 44 (end of treatment/early termination [ET]) of the open-label extension study; patients were contacted via telephone for safety follow-up at Week 45 (study exit)
- Vision blurred, mydriasis, and symptoms related to urinary retention/hesitation were prespecified as TEAEs of special interest (AESIs) based on known association with anticholinergic compounds and potential for serious medical consequences
- Dose interruptions were allowed for intolerable treatment-related TEAEs and mandated for treatment-related vision blurred and urinary retention/hesitancy-related symptoms
- Patients with symptoms suggestive of urinary retention were to be evaluated regarding its clinical course; for symptoms of obstruction, patients were to be referred to a urologist or for emergency care
- Patients who reported vision blurred were to be carefully evaluated to determine if the patient inadvertently touched the eye(s) after application of study drug
  - If there was no history of inadvertent introduction of study drug into the eye, the patient was to be evaluated to rule out any serious acute condition
  - If the vision blurred continued for >24 hours, the patient was to be evaluated by an ophthalmologist or referred to emergency care
- Analyses were conducted using ARIDO data to examine the incidence and timing of TEAEs and AESIs as well as discontinuation due to adverse events and management of AESIs
- All safety analyses were performed on the safety population (patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in the open-label extension)

RESULTS

Patient Disposition and Demographics

- A total of 564/651 (86.6%) patients entered the open-label extension
  - Of the 564 enrolled patients, 13 had no post-baseline assessment and 1 did not receive study drug; therefore, the safety population comprised 550 patients (55.3% female, 83.3% white, mean age of 33.0 years) (**Table 1**)

Table 1. Patient Demographics and Baseline Disease Characteristics (Baseline of Randomized Control Trials)

	GT (N=550)
Demographics	
Age (years), mean ± SD	33.0 ± 11.4
Age group, n (%)	
≥16 years	28 (5.1)
<16 years	522 (94.9)
Female, n (%)	304 (55.3)
White, n (%)	458 (83.3)
Body mass index (kg/m²), mean ± SD	27.3 ± 5.0
Baseline Disease Characteristics	
Sweat production (mg/5 min)[a]	
Mean ± SD	164.7 ± 145.0
Median	116.9
HDSS, n (%)[b,c]	
Grade 3	348 (63.3)
Grade 4	201 (36.5)
DLQI, mean ± SD[d]	11.4 ± 5.9
CDLQI, mean ± SD[e]	8.9 ± 5.4

[a]Gravimetrically measured average from the left and right axillae
[b]HDSS grade ≥3 was an inclusion criterion
[c]N=549; 1 patient entered ATMOS-2 with HDSS=2, which was a protocol violation
[d]Patients >16 years of age
[e]Patients ≤16 years of age
The safety population includes patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in the open-label extension
CDLQI, children's DLQI; DLQI, Dermatology Life Quality Index; GT Glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; SD standard deviation

Summary of TEAEs and AESIs

- Most patients experiencing TEAEs in the open-label extension had mild or moderate events (>90%) (**Table 2**), which is consistent with safety results in the double-blind trials
- AESI incidence over 44 weeks (14.2% [78/550]) was similar to that in the double-blind trials (13.3% [61/459])
  - AESIs predominantly were vision blurred (37 [6.7%]), mydriasis (29 [5.3%]), and urinary hesitation (23 [4.2%])
  - Most AESIs experienced by patients were mild or moderate and resolved within 3 to 14 days after onset

Table 2. Safety Overview and TEAEs in the Open-Label Trial to Week 45/EOS

n (%)	GT (N=550)
Any TEAE	329 (59.8)
Any serious TEAE	7 (1.3)[a]
Discontinuation due to a TEAE	44 (8.0)
Deaths	0
TEAEs reported in ≥5% of patients	
Dry mouth	93 (16.9)[b]
Vision blurred	37 (6.7)[b,c]
Application site pain	35 (6.4)
Nasopharyngitis	32 (5.8)
Mydriasis	29 (5.3)[b,d]
Anticholinergic TEAEs reported in >2% of patients	
Dry mouth	93 (16.9)[b]
Vision blurred	37 (6.7)[b,c]
Mydriasis	29 (5.3)[b,d]
Urinary hesitation	23 (4.2)
Nasal dryness	20 (3.6)
Dry eye	16 (2.9)
	Any TEAEs (N=329)
TEAE by intensity	
Mild	148 (45.0)
Moderate	153 (46.5)
Severe	28 (8.5)
Relation to study drug	
Not related	131 (39.8)
Related	198 (60.2)

[a]Infectious colitis, affective disorder, suicide attempt, unilateral mydriasis, chest pain, concussion, diverticulitis; only mydriasis was considered by the Investigator as related to treatment (dose was not changed but patient withdrew from study due to moving domiciles)
[b]Dry mouth, vision blurred, and mydriasis appear twice in the table as they meet criteria for common TEAEs and are also associated with anticholinergic use
[c]37 patients reported a total of 45 vision blurred events; 40 (88.9%) were bilateral
[d]29 patients reported a total of 37 mydriasis events; 31 (83.8%) were unilateral
Safety outcomes from the first application of study drug in the open-label trial are reported; the safety population includes patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in the open-label extension
Numbers in table represent the number of patients reporting ≥1 TEAE
EOS, end of study; GT, Glycopyrronium tosylate; TEAE, treatment-emergent adverse event

Timing of TEAE and AESI Onset

- In the open-label extension, the onset of TEAEs occurred mainly in the first 12 weeks and decreased thereafter (**Table 3**)
  - 32.0% of patients experienced TEAEs from Weeks 0 to 4 (N=550)
  - 27.6% of patients experienced TEAEs from Weeks 5 to 12 (N=537)
  - 16.2% of patients had TEAEs from Week 36 to the end-of-study (N=365)
- The percentage of patients who experienced the most common TEAE, dry mouth, decreased throughout the study (**Table 3**)
  - 10.7% Weeks 0 to 4 (N=550)
  - 4.3% Weeks 5 to 12 (N=537)
  - 1.4% Week 36 to end-of-study (N=365)
- The proportion of patients who reported AESIs also decreased over the course of the open-label extension (**Table 3**)

Table 3. TEAEs By Time of Onset in the Open-Label Trial to Week 45/EOS (Safety Population[a])

TEAEs, n (%)	0 to 4 weeks (N=550)	>4 to 12 weeks (N=537)	>12 to 24 weeks (N=479)	>24 to 36 weeks (N=417)	>36 weeks to EOS (N=365)
Any TEAE	176 (32.0)	148 (27.6)	102 (21.3)	78 (18.7)	59 (16.2)
Drug withdrawals due to TEAE	21 (3.8)	14 (2.6)	12 (2.5)	3 (0.7)	1 (0.3)
TEAEs reported in >5% of patients[b]					
Dry mouth	59 (10.7)	23 (4.3)	19 (4.0)	15 (3.6)	5 (1.4)
Vision blurred	11 (2.0)	14 (2.6)	7 (1.5)	5 (1.2)	4 (1.1)
Application site pain	16 (2.9)	9 (1.7)	5 (1.0)	6 (1.4)	3 (0.8)
Nasopharyngitis	14 (2.5)	9 (1.7)	4 (0.8)	5 (1.2)	3 (0.8)
Mydriasis[c]	8 (1.5)	8 (1.5)	9 (1.9)	5 (1.2)	2 (0.5)
AESIs					
Vision blurred	11 (2.0)	14 (2.6)	7 (1.5)	5 (1.2)	4 (1.1)
Mydriasis[c]	8 (1.5)	8 (1.5)	9 (1.9)	5 (1.2)	2 (0.5)
Urinary hesitation	14 (2.5)	4 (0.7)	4 (0.8)	2 (0.5)	1 (0.3)
Nocturia	2 (0.4)	0	0	0	0
Urine flow decreased	1 (0.2)	1 (0.2)	0	0	0
Hypermetropia[d]	0	0	0	1 (0.2)	0
Pollakiuria	0	0	0	1 (0.2)	0
Pupils unequal[d]	1 (0.2)	0	0	0	0

[a]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
[b]Based on cumulative total at end of study
[c]29 patients reported a total of 37 mydriasis events; 31 (83.8%) were unilateral
[d]The MedDRA preferred terms that were pre-specified as TEAEs of special interest were vision blurred, mydriasis, pupils unequal, hypermetropia and the following terms for symptoms of urinary hesitancy/retention: nocturia, pollakiuria, urinary hesitation, urinary retention, urinary obstruction, and urine flow decreased.
Numbers in table represent the number of patients reporting ≥1 TEAE, not number of events
Rates of discontinuation due to TEAEs were 0.2% at Week 1 and 0.3% at Week 44 when evaluating patients by visit and accounting for all patients who entered the study
AESI, prespecified anticholinergic TEAE of special interest; EOS, end of study; TEAE, treatment-emergent adverse event

Discontinuation due to TEAEs

- Rates of drug withdrawal due to TEAEs remained low and relatively stable throughout the open-label extension (**Table 3**), with a cumulative total of 8.0% (44 of 550 patients) over 44 weeks (**Tables 2 and 3**)
- Most anticholinergic adverse events infrequently led to discontinuation in the open-label extension, consistent with the double-blind trials (**Table 4**)

Table 4. Discontinuation due to Anticholinergic TEAEs Over Time to Week 45/EOS (Safety Population[a])

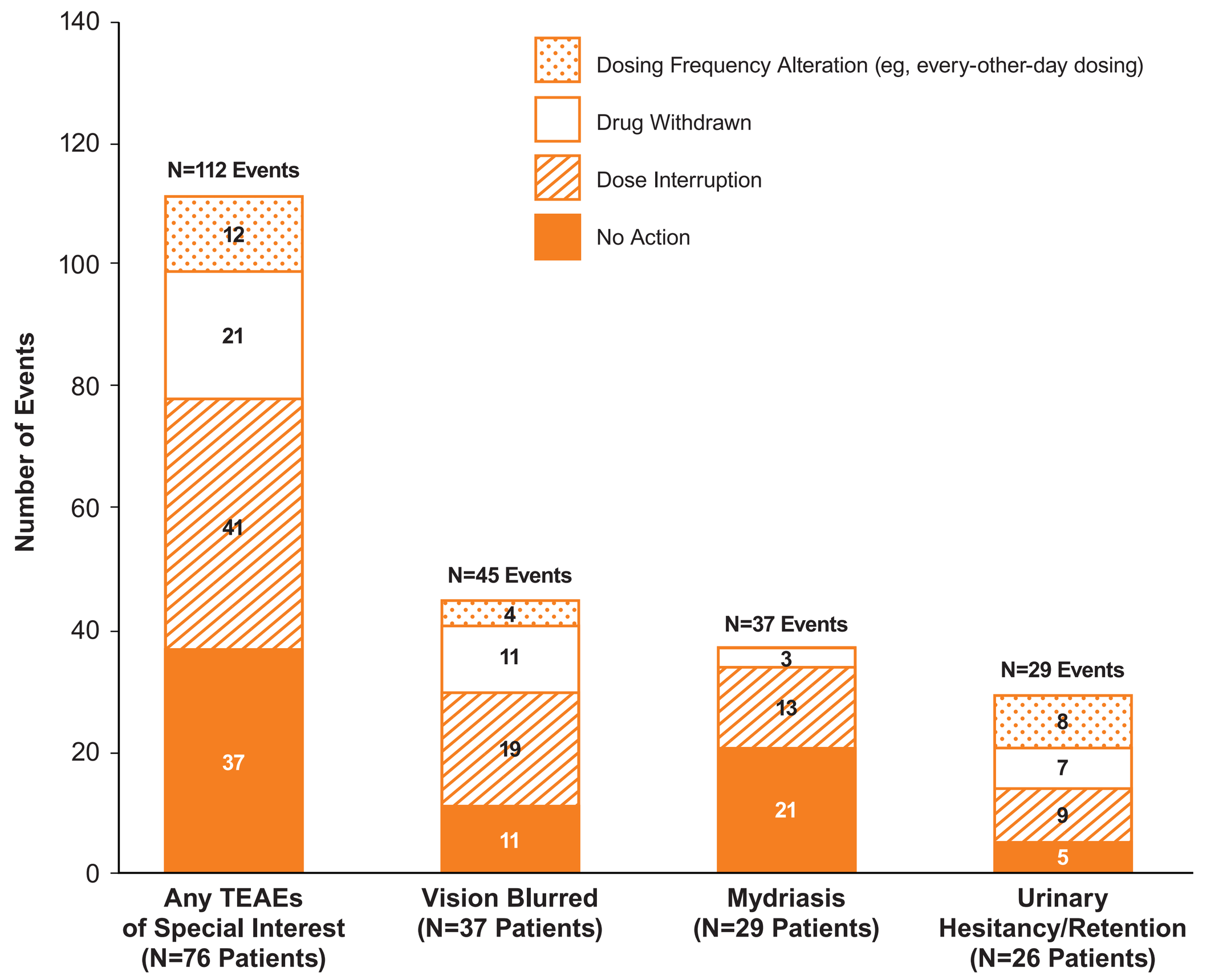
n (%)	0 to 4 weeks N=550	>4 to 12 weeks N=537	>12 to 24 weeks N=479	>24 to 36 weeks N=417	>36 weeks to EOS N=365
Discontinuation due to Anticholinergic TEAEs					
Dry eye	2 (0.4%)	0	1 (0.2%)	1 (0.2%)	0
Mydriasis	2 (0.4%)	0	0	0	0
Vision blurred	3 (0.5%)	3 (0.6%)	3 (0.6%)	1 (0.2%)	0
Dry mouth	3 (0.5%)	2 (0.4%)	2 (0.4%)	2 (0.5%)	0
Urinary hesitation	3 (0.5%)	0	1 (0.2%)	1 (0.2%)	0
Nasal dryness	3 (0.5%)	0	0	1 (0.2%)	0
Constipation	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	0

[a]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
Numbers in table represent the number of patients, not number of events
EOS, end of study; TEAE, treatment emergent adverse event

Management of AESIs

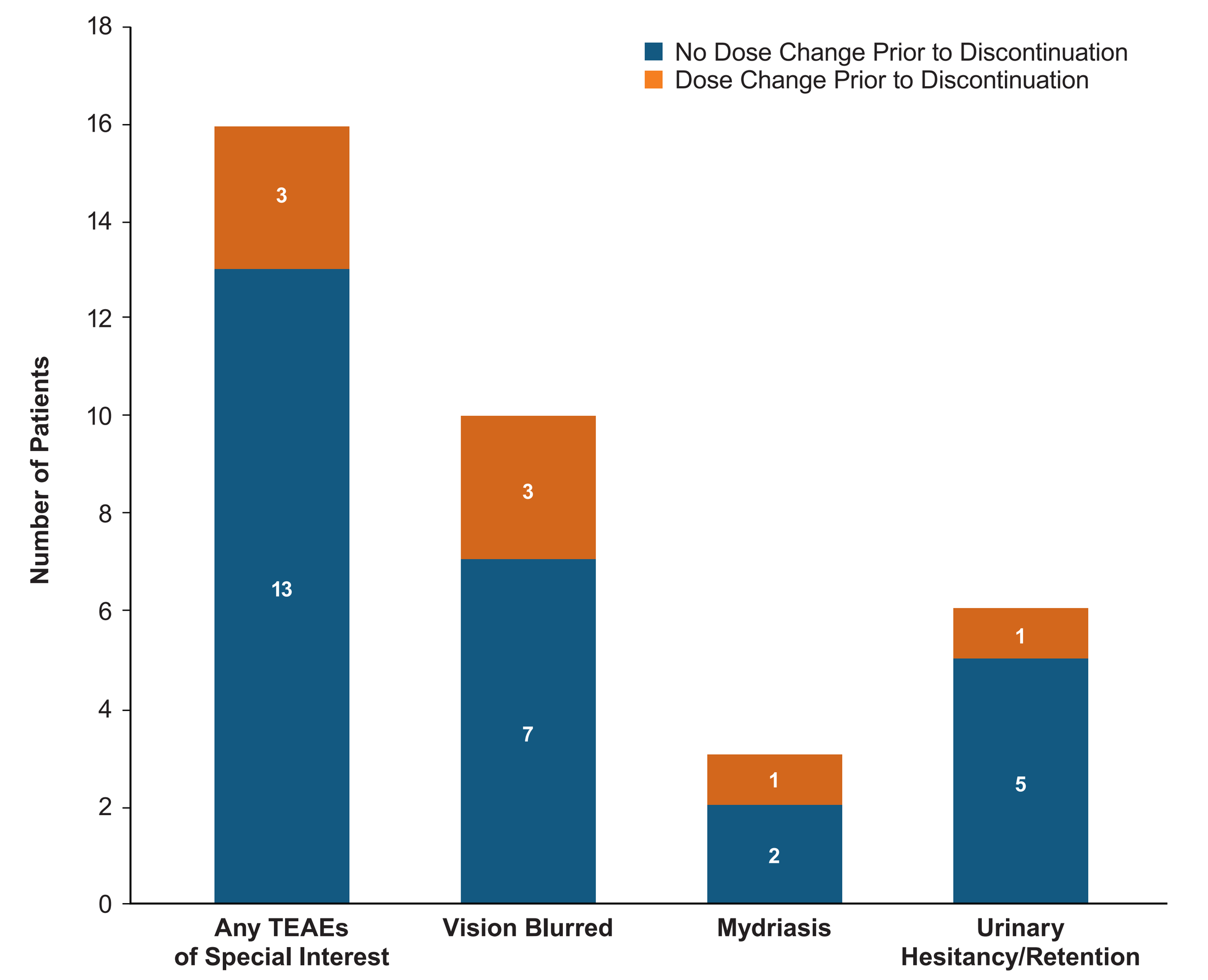
- Management of AESIs included dose interruption (eg, interruption of GT application for a period of time), dosing frequency alteration (eg, every-other-day dosing), drug withdrawal, and no action (**Figure 2**)
- AESIs infrequently led to discontinuation/drug withdrawal (**Table 4 and Figure 2**), and most events were managed by dose interruption or no action (**Figure 2**) and resolved within 3 to 14 days of onset; a similar trend was observed in the double-blind lead-in trials[4]
- Most of the patients who discontinued the study due to an AESI did not have a dose reduction or dosing frequency alteration prior to discontinuation (**Figure 3**)

Figure 2. Management of AESI Events in the Open-Label Trial (Safety Population, N=500)



The MedDRA preferred terms that were pre-specified as TEAEs of special interest were vision blurred, mydriasis, pupils unequal, hypermetropia and the following terms for symptoms of urinary hesitancy/retention: nocturia, pollakiuria, urinary hesitation, urinary retention, urinary obstruction, and urine flow decreased. Though dry mouth is often associated with anticholinergic use, it was not designated as one of the prespecified TEAEs of special interest and is not refelected in this figure. Patients may have had more than 1 TEAE of special interest. Safety outcomes from the first application of study drug in the open-label trial are reported. The safety population includes patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in the open-label extension.
AESI, prespecified adverse event of special interest

Figure 3. Prior Management in Those Discontinuing Due to AESIs



The MedDRA preferred terms that were pre-specified as TEAEs of special interest were vision blurred, mydriasis, pupils unequal, hypermetropia and the following terms for symptoms of urinary hesitancy/retention: nocturia, pollakiuria, urinary hesitation, urinary retention, urinary obstruction, and urine flow decreased. Patients may have had more than 1 TEAE of special interest
AESI, prespecified adverse event of special interest

CONCLUSIONS

- GT applied once-daily for up to 48 weeks (4 weeks double-blind + 44 weeks open-label) was generally well tolerated, consistent with the safety profile observed in prior phase 3 studies
  - TEAEs, including those associated with anticholinergic activity, were mostly mild/moderate, with a decreasing incidence over time, and infrequently led to discontinuation
  - A reduction in TEAEs reported over time throughout the trial may be due to a number of factors, including discontinuation of patients who experienced TEAEs, increased time length between visits, increased patient experience with drug application, and/or acclimation to adverse events
  - Overall discontinuation due to AESIs was low, and dose interruption, dosing frequency alteration, as well as no changes to dosing were effective ways to manage these events
- Topical, once-daily GT provides a noninvasive, effective treatment option for primary axillary hyperhidrosis

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AUTHOR DISCLOSURES

DMP: Consultant and investigator for Dermira, Inc. **JD, RG:** Employee of Dermira, Inc. **AH:** Consultant for Dermira, Inc.; employee of the University of Texas Medical School, Houston, which received compensation from Dermira, Inc. for study participation.

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