Clinical Management of Anticholinergic Adverse Events with Glycopyrronium Cloth, a Treatment for Primary Axillary Hyperhidrosis

Authors: D. Pariser,[1] R. Gopalan,[2] J. Drew,[2] L. Green[3]

[1]Eastern Virginia Medical School and Virginia Clinical Research, Inc., Norfolk, VA; [2]Dermira, Inc., Menlo Park, CA; [3]George Washington University School of Medicine, Washington, DC

INTRODUCTION

- Hyperhidrosis affects an estimated 4.8% of the US population, or approximately 15.3 million people, and negative psychological consequences (eg, anxiety, depression) are associated with the disorder[1]
- The impact of hyperhidrosis on quality of life is comparable to, or greater than, the impact of psoriasis or eczema[2]
- Glycopyrronium tosylate (GT) is a topical anticholinergic approved in the US for primary axillary hyperhidrosis in patients 9 years and older (glycopyrronium cloth, 2.4%, for topical use)
- GT safety and efficacy were evaluated in two, replicate, randomized, phase 3 clinical trials (ATMOS-1 and ATMOS-2); the primary efficacy and safety results of these studies have been previously reported, and in these trials, GT reduced sweating severity and sweat production compared to vehicle and was generally well tolerated[3]

OBJECTIVE

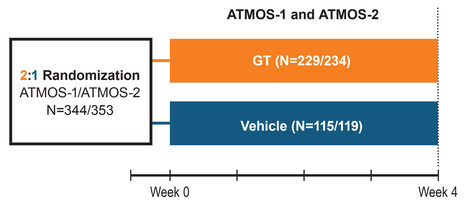
- To examine the safety and tolerability profile of GT in the ATMOS-1 and ATMOS-2 trials and how treatment-emergent adverse events (TEAEs) associated with anticholinergic compounds were managed/resolved during those trials

METHODS

ATMOS-1 and ATMOS-2 Study Design and Patients

- ATMOS-1 (NCT02530281; sites in the US and Germany) and ATMOS-2 (NCT02530294; US sites only) were replicate, randomized, parallel-group, 4-week, double-blind, phase 3 clinical trials[3] (**Figure 1**)
- Patients with primary axillary hyperhidrosis were randomized (2:1) to GT 3.75% topical solution (equivalent to 2.4% glycopyrronium) or vehicle applied once daily to each axilla
- Eligible patients were ≥9 years of age (patients <16 years were only recruited at US sites), had primary axillary hyperhidrosis for ≥6 months, gravimetrically-measured sweat production of ≥50 mg/5 min in each axilla, Axillary Sweating Daily Diary (ASDD) sweating severity (Item 2)[4] score ≥4, and Hyperhidrosis Disease Severity Scale (HDSS) grade ≥3
- Patients were excluded for history of a condition that could cause secondary hyperhidrosis; prior surgical procedure or treatment with a medical device for axillary hyperhidrosis; treatment with iontophoresis within 4 weeks or treatment with botulinum toxin within 1 year for axillary hyperhidrosis; axillary use of nonprescription antiperspirants within 1 week or prescription antiperspirants within 2 weeks; new or modified psychotherapeutic medication regimen within 2 weeks; and/or treatment with medications having systemic anticholinergic activity, centrally acting alpha-2 adrenergic agonists, or beta-blockers within 4 weeks unless dose had been stable ≥4 months and was not expected to change

Figure 1. Study Design



GT, topical glycopyrronium tosylate

Assessments

- Coprimary endpoints assessed at Week 4 were ASDD Item 2 responder rate (≥4-point improvement from Baseline) and mean absolute change from Baseline in gravimetrically-measured sweat production (average of both axillae)
- TEAEs, including relationship to study drug, were recorded throughout the trial
  - 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
- Blurred vision, mydriasis, and symptoms associated with urinary retention/hesitation were identified as TEAEs of special interest based on their known association with anticholinergic compounds
- Dose interruptions were allowed for intolerable treatment-related adverse events and mandated for treatment-related blurred vision and symptoms associated with urinary hesitancy, obstruction or retention (study drug was to be subsequently resumed based on clinical judgment)
- Patients with symptoms suggestive of urinary retention were to be evaluated for its clinical course; for symptoms of obstruction, patients were to be referred to a urologist or for emergency care
- Patients who complained of blurred vision 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 blurred vision continued for >24 h, the patient was to be evaluated by an ophthalmologist or referred to emergency care

RESULTS

- In the pooled population of ATMOS-1 and ATMOS-2, 463 patients were randomized to GT and 234 to vehicle; 426 (92.0%) and 225 (96.2%) completed the trials, respectively
- Individual trial and pooled data for GT versus vehicle showed significantly higher ASDD Item 2 response rates (≥4-point improvement in sweating severity) and reduced sweat production at Week 4 compared to Baseline (coprimary endpoints)[3]

Treatment-Emergent Adverse Events

- The frequency of TEAEs in the pooled population (56.0% GT, 32.3% vehicle) was similar to the individual trials (ATMOS-1: 54.2% GT, 28.9% vehicle; ATMOS-2: 57.8% GT, 35.6% vehicle)
- Consistent with individual studies, TEAEs in the pooled population were mostly mild or moderate in severity, transient, and infrequently led to discontinuation (**Table 1**)
- Commonly reported TEAEs (≥5% of patients) in the GT group included some events associated with anticholinergic activity (dry mouth [24.2% GT, 5.6% vehicle] and mydriasis [6.8% GT, 0% vehicle]); other common TEAEs were application site pain (8.7% GT, 9.5% vehicle), oropharyngeal pain (5.7% GT, 1.3% vehicle) and headache (5.0% GT, 2.2% vehicle) (**Table 1**)

TEAEs Leading to Drug Interruption or Dose Reduction (eg, Every-Other-Day Dosing)

- A total of 6.3% of patients in the GT group and 2.2% of patients in the vehicle group experienced TEAEs that led to drug interruptions during the trials (**Table 1**)
  - In the GT group, the most common TEAEs that led to drug interruptions were dry mouth and mydriasis (9 patients [1.9%] each), urinary hesitation (6 patients [1.3%]), vision blurred (5 patients [1.1%]), and headache, oropharyngeal pain, and constipation (2 patients [0.4%] each)
  - In the vehicle group, TEAEs that led to drug interruptions most commonly included application site pain and application site irritation (2 patients [0.9%] each)
- A total of 5.2% of patients in the GT group and 0 patients in the vehicle group experienced TEAEs that led to dose reduction (eg, every-other-day dosing) during the trials (**Table 1**)
  - In the GT group, the most common TEAEs that led to dose reduction were dry mouth (15 patients [3.3%]), dry eye (3 patients [0.7%]), pruritus and urinary hesitation (2 patients [0.4%] each)
- All TEAEs leading to drug interruptions or dose reductions were mild or moderate

Table 1. Safety Overview and TEAEs Through Week 4 in ATMOS-1 and ATMOS-2 (Pooled Safety Population)

n (%)	Vehicle (N=232)	GT (N=459)
TEAEs		
Any	75 (32.3)	257 (56.0)
Drug-related	38 (16.4)	179 (39.0)
Serious[a]	0	2 (0.4)[b]
Led to drug interruption	5 (2.2)	29 (6.3)
Led to dose reduction (eg, every-other-day dosing)	0	24 (5.2)
Discontinuations due to TEAE	1 (0.4)	17 (3.7)
Deaths	0	0
TEAEs by intensity		
Mild	53 (22.8)	170 (37.0)
Moderate	22 (9.5)	83 (18.1)
Severe	0	4 (0.9)
Common TEAEs reported in ≥5% of patients in either treatment arm in pooled population		
Dry mouth[c]	13 (5.6)	111 (24.2)
Application site pain	22 (9.5)	40 (8.7)
Mydriasis[c]	0	31 (6.8)
Oropharyngeal pain	3 (1.3)	26 (5.7)
Headache	5 (2.2)	23 (5.0)
Anticholinergic TEAEs reported in >2% of patients in either treatment arm in ATMOS-1 or ATMOS-2		
Dry mouth[c]	13 (5.6)	111 (24.2)
Mydriasis[c]	0	31 (6.8)
Urinary hesitation	0	16 (3.5)
Dry eye	1 (0.4)	11 (2.4)
Blurred vision	0	16 (3.5)
Nasal dryness	1 (0.4)	12 (2.6)
Constipation	0	9 (2.0)
Urinary retention	0	7 (1.5)

[a]Serious TEAEs: ATMOS-1: Moderate unilateral mydriasis, considered related to study drug; ATMOS-2: Moderate dehydration, considered not related to study drug
[b]Serious TEAEs are those that: resulted in death, were immediately life threatening, required inpatient hospitalization, resulted in persistent or significant disability, or judged to require medical/surgical attention in order to avoid any of the previously mentioned outcomes
[c]Mydriasis and dry mouth appear twice in the table since they meet criteria for common TEAEs and are associated with anticholinergic use
GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

TEAEs of Special Interest

- TEAEs of special interest (blurred vision, mydriasis, and symptoms associated with urinary retention/hesitation) occurred in 13.3% (61/459) of GT-treated patients and no vehicle-treated patients (**Table 2**)
  - Most were considered related to study drug, of mild to moderate severity, and transient
  - Severe TEAEs of special interest occurred in only one subject who had both severe mydriasis and severe urinary retention; these events, along with mild blurred vision and TEAEs of dry mouth (severe) and anhidrosis (severe), led to discontinuation, and all resolved after study drug withdrawal
  - One subject had a serious TEAE of unilateral mydriasis of moderate severity; given a head injury the prior week, the subject was hospitalized to rule out a central nervous system disorder, and the event resolved after study drug withdrawal
- Among the 6.8% of pooled GT-treated patients experiencing mydriasis, most events were unilateral (74.2% [23/31]), while most blurred vision events were bilateral (68.8% [11/16]); treatment was not discontinued in most cases (**Table 2**)
- In general, TEAEs of special interest resolved within 3-14 days, despite continued application of study drug or, did not recur upon treatment resumption
  - The duration of adverse events could be self-reported by patients but also could be noted as part of a symptom directed physical exam
  - A total of 80 events of TEAEs of special interest occurred in 61 patients; nine of these events (9/80 [11.3%]) lasted for >14 days and included 3 events of vision blurred, 2 events of urinary hesitation, and single events of mydriasis, nocturia, pollakiuria, and urinary retention

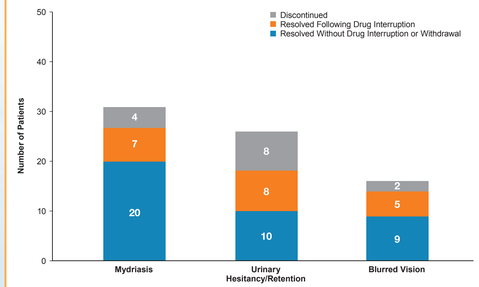
Table 2. TEAEs of Special Interest

n (%)	Vehicle (N=232)	GT (N=459)
Mydriasis	0	31 (6.8)
Led to discontinuation	--	4 (0.9)
Blurred vision	0	16 (3.5)
Led to discontinuation	--	2 (0.4)
Urinary hesitancy/retention	0	26 (5.7)
Urinary hesitation Led to discontinuation	0 --	16 (3.5) 3 (0.7)
Urinary retention Led to discontinuation	0 --	7 (1.5) 4 (0.9)
Urine flow decreased Led to discontinuation	0 --	3 (0.7) 1 (0.2)
Dysuria[a]	0	1 (0.2)
Nocturia	0	1 (0.2)
Pollakiuria	0	1 (0.2)

[a]This patient had symptoms of urinary hesitation, but the event was coded as dysuria and not reported as a TEAE of special interest
GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

- Most TEAEs of special interest resolved without any drug interruption or withdrawal (**Figure 2**)
  - For patients with mydriasis or blurred vision, over half had the event resolve without study drug interruption or discontinuation
  - Eight patients had both mydriasis and blurred vision (all concurrent), and for 6 of 8 patients, the events resolved during drug interruption or following discontinuation
- In general, TEAEs of special interest did not recur upon treatment resumption
  - One patient had a drug interruption due to mydriasis; the mydriasis resolved but recurred a week later

Figure 2. Resolution of TEAEs of Special Interest



Patients may have had more than one TEAE of special interest, and ≥1 TEAE of special interest may have led to discontinuation. Urinary hesitancy/retention includes urinary hesitation, urinary retention, urine flow decreased, dysuria, nocturia, and pollakiuria
TEAE, treatment-emergent adverse event

CONCLUSIONS

- In two large, phase 3, double-blind, vehicle-controlled trials, GT was well tolerated and only 3.7% (GT) and 0.4% (vehicle) of patients discontinued due to a TEAE
- TEAEs were mostly mild or moderate in severity and transient
- Clinical management of TEAEs included drug interruption (6.3% GT, 2.2% vehicle) and drug reduction (5.2% GT, 0 vehicle)
- Anticholinergic events of blurred vision, mydriasis, and urinary hesitancy/retention occurred infrequently; when anticholinergic events did occur, onset was most often early, and most events resolved without interruption or withdrawal of GT treatment
- Assessment of TEAE management in the open-label extension trial will continue to inform clinical practice

REFERENCES

1. Doolittle et al. *Arch Dermatol Res.* 2016; 308 (10):743-9. **2.** Spalding et al. *Value Health.* 2003;6(3);242. **3.** Glaser et al. *J Am Acad Dermatol.* 2018. In press. **4.** Glaser et al. *J Clin Aesthet Dermatol.* 2018;11(5 Suppl):S16-17 (Abstract).

ACKNOWLEDGEMENTS

These studies were funded by Dermira, Inc. Medical writing support was provided by Prescott Medical Communications Group (Chicago, IL) with financial support from Dermira, Inc.

DISCLOSURES

DMP: Consultant and Investigator for Dermira, Inc. **RG & JD**: Employees of Dermira, Inc. **LG**: Investigator for Brickell; Advisory Board member and Investigator for Dermira.

Poster presented at the 37th Fall Clinical Dermatology Conference | Las Vegas, NV | October 18-21, 2018