Long-Term Response with Topical Glycopyrronium Tosylate in Patients with Primary Axillary Hyperhidrosis According to Double-Blind Treatment Group

E.L. Lain,[1] D.A. Glaser,[2] R. Gopalan,[3] V. Yan,[3] J. Drew,[3] D.M. Pariser[4]

[1]Austin Institute for Clinical Research, Austin, TX; [2]Saint Louis University, St. Louis, MO; [3]Dermira, Inc., Menlo Park, CA; [4]Eastern Virginia Medical School and Virginia Clinical Research, Inc., Norfolk, VA

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, 4-week, vehicle (VEH)-controlled phase 3 trials (ATMOS-1 [NCT02530281], ATMOS-2 [NCT02530294])[2,3]
  - GT improved sweating severity, reduced sweat production, and improved quality of life in these trials
- Long-term safety and descriptive efficacy of GT were evaluated in an open-label, 44-week extension (ARIDO [NCT02553798]) of the two double-blind trials

OBJECTIVE

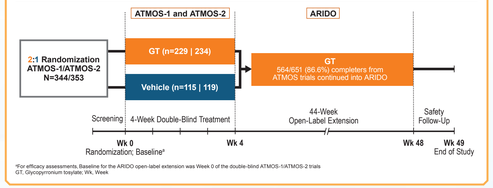
To compare long-term safety and efficacy in patients remaining on GT into the open-label extension (GT→GT) to patients newly exposed to GT in the open-label extension (VEH→GT)

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 double-blind 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**)
  - Patients eligible for the double-blind lead-in trials were ≥9 years of age (only patients aged ≥18 years were recruited at German 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)/ASDD-Children (ASDD-C) patient-reported sweating severity (Item 2) score ≥4 (numeric scale 0-10), 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 based 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

- Though the primary outcome of the open-label extension was long-term safety, descriptive efficacy assessments included two outcomes from the double-blind trials
  - HDSS responder rate (≥2-grade improvement from Baseline)
  - Dermatology Life Quality Index (DLQI) change from Baseline (cfB) to Week 4 (end of double-blind) and to Week 20 and Week 44/ET of open-label (up to Week 48 total GT treatment [4 weeks double-blind + 44 weeks open-label extension])
- Safety outcomes included treatment-emergent adverse events (TEAEs)
- Efficacy and safety outcomes in the open-label extension were analyzed post hoc according to double-blind treatment assignment
- TEAEs and HDSS were assessed on Day 1 (Week 4 of the double-blind trials) and Weeks 2, 4, 8, 12, 16, 20, 28, 36, and 44/ET (end of treatment/early termination); DLQI was assessed on Day 1 (Week 4 of the double-blind trials) and Weeks 20 and 44/ET of the open-label extension; patients were contacted via telephone for safety follow-up at Week 45 (study exit)

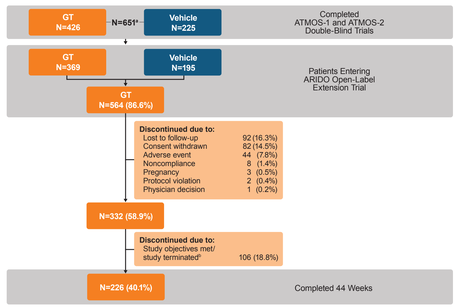
Analyses

- Safety and efficacy analyses were conducted in the safety population (patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO)
- No imputation for missing data was performed

RESULTS

- A total of 564/651 (86.6%) patients entered the open-label extension (n=369 GT, n=195 VEH) (**Figure 2**); of these, 13 had no post-Baseline assessment and 1 did not receive study drug; therefore, the safety population included 550 patients (55.3% female, 83.3% white, mean age 33 years; **Table 1**)
  - 332 (58.9%) were in the trial at early study termination
  - 226 (40.1%) completed Week 44 of the open-label extension (n=143 GT→GT, n=83 VEH→GT)
- At Baseline of the double-blind trials, demographics and disease characteristics were similar across treatment arms (**Table 1**)
- At Baseline of the open-label extension (Week 4 of the double-blind trials), patients who had been on GT during the double-blind trials (GT→GT) had lower sweat production, HDSS, and DLQI/CDLQI scores than patients who had been treated with vehicle for the previous 4 weeks (VEH→GT) (**Table 2**)

Figure 2. Patient Disposition



GT, Glycopyrronium tosylate
[a]651 of 697 patients (93.4%) randomized to treatment in ATMOS-1 and ATMOS-2 completed study
[b]Sponsor terminated study early, per protocol, when study objective of 100 patients receiving treatment for at least 12 months was achieved

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

	GT→GT N=361	VEH→GT N=189	Total N=550
Demographics			
Age (years), mean ± SD	32.6 ± 11.0	33.9 ± 12.3	33.0 ± 11.4
Age group, n (%) <16 years ≥16 years	15 (4.2) 346 (95.8)	13 (6.9) 176 (93.1)	28 (5.1) 522 (94.9)
Female, n (%)	206 (57.1)	98 (51.9)	304 (55.3)
White, n (%)	297 (82.3)	161 (85.2)	458 (83.3)
Body mass index (kg/m²), mean ± SD	27.1 ± 5.0	27.6 ± 4.8	27.3 ± 5.0
Baseline Disease Characteristics			
Sweat production (mg/5 min)[a] Mean ± SD Median	159.1 ± 132.6 122.1	175.3 ± 165.9 114.8	164.7 ± 145.0 116.9
HDSS, n (%)[b,c] Grade 3 Grade 4	225 (62.3) 136 (37.7)	123 (65.1) 65 (34.4)	348 (63.3) 201 (36.5)
DLQI, mean ± SD[d]	11.9 ± 5.9	10.6 ± 6.0	11.4 ± 5.9
CDLQI, mean ± SD[e]	9.4 ± 5.1	8.2 ± 5.9	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 ARIDO-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; GT→GT, patients assigned to GT in the double-blind trials who continued on GT in the open-label extension; HDSS, Hyperhidrosis Disease Severity Scale; SD, standard deviation; VEH, vehicle; VEH→GT, patients assigned to VEH in the double-blind trials who were newly exposed to GT in the open-label extension

Table 2. Baseline Disease Characteristics (Baseline of Open-Label Trial)

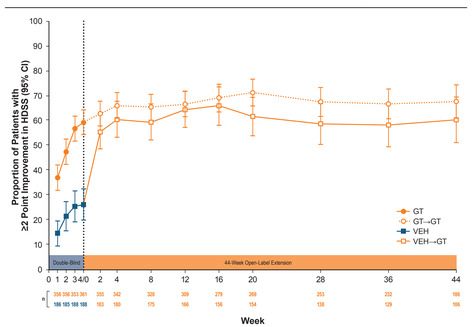
	GT→GT N=361	VEH→GT N=189	Total N=550
Sweat production (mg/5 min) Mean ± SD[a] Median Min to max	51.1 ± 90.0 29.0 0.5 to 1179	85.1 ± 98.6 57.0 3.4 to 804.4	62.8 ± 94.3 36.7 0.5 to 1179
HDSS, n (%)[b] Grade 1 Grade 2 Grade 3 Grade 4	149 (41.3) 172 (47.6) 30.0 (8.3) 10.0 (2.8)	26 (13.8) 83 (43.9) 59.0 (31.2) 21.0 (11.1)	175 (31.8) 255 (46.4) 89.0 (16.2) 31.0 (5.6)
DLQI, mean ± SD[c]	3.3 ± 4.3	6.1 ± 5.7	4.2 ± 5.0
CDLQI, mean ± SD[d]	1.6 ± 2.1	6.4 ± 7.3	3.7 ± 5.5

[a]Gravimetrically measured average from the left and right axillae
[b]Total N=549; 1 patient entered ARIDO-2 with HDSS=2, which was a protocol violation
[c]Patients >16 years of age
[d]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; GT→GT, patients assigned to GT in the double-blind trials who continued on GT in the open-label extension; HDSS, Hyperhidrosis Disease Severity Scale; SD, standard deviation; VEH, vehicle; VEH→GT, patients assigned to VEH in the double-blind trials who were newly exposed to GT in the open-label extension

HDSS Responder Rate

- At the end of the double-blind trials, 59.3% (GT) vs 26.1% (VEH) of those entering the open-label extension had achieved HDSS response (**Figure 3**)
- By Week 2 of the open-label extension, HDSS responder rate was 62.8% for GT→GT vs 55.7% for VEH→GT, and 95% confidence intervals overlapped, representing a marked increase over VEH response for patients who were newly exposed to GT (**Figure 3**)
- HDSS responder rate was maintained over the course of the open-label extension for both groups (**Figure 3**)

Figure 3. HDSS Responder Rate (≥2-Grade Improvement from Baseline[a]) to Week 44/ET by Double-Blind Treatment Assignment

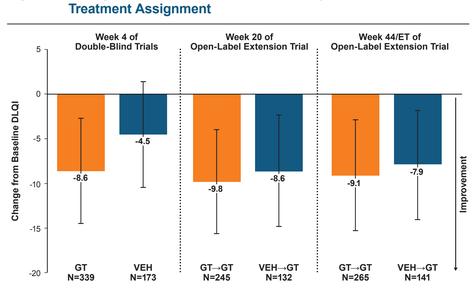


[a]Baseline of ATMOS-1/ATMOS-2 for vehicle-treated and GT-treated patients who continued into ARIDO and received GT treatment thereafter
The safety population includes patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in the open-label extension; there was no imputation of missing values
CI, confidence interval; ET, end of treatment/early termination; GT, Glycopyrronium tosylate; GT→GT, patients assigned to GT in the double-blind trials who continued on GT in the open-label extension; HDSS, Hyperhidrosis Disease Severity Scale; VEH→GT, patients assigned to vehicle in the double-blind trials who were newly exposed to GT in the open-label extension

DLQI Score

- At the end of the double-blind trials, patients entering the open-label extension who had received GT in the double-blind trials had a greater decrease (improvement) from Baseline in DLQI score (mean ± SD, -8.6 ± 5.9) than those who had received VEH in the double-blind trials (-4.5 ± 6.0) (**Figure 4**)
- By Week 20 of the open-label extension, patients newly exposed to GT (VEH→GT) showed a similar improvement from Baseline in mean DLQI score (-8.6 ± 6.24) as patients who remained on GT throughout the trials (GT→GT; -9.8 ± 5.84); this improvement was maintained at Week 44/ET (-7.9 ± 6.16 for VEH→GT and -9.1 ± 6.26 for GT→GT, **Figure 4**)

Figure 4. Change from Baseline[a] in DLQI Score[b] by Double-Blind Treatment Assignment



[a]Baseline in ATMOS-1/ATMOS-2
[b]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
DLQI, Dermatology Life Quality Index; ET, end of treatment/early termination; GT, Glycopyrronium tosylate; GT→GT, patients assigned to GT in the double-blind trials who continued on GT in the open-label extension; VEH, vehicle; VEH→GT, patients assigned to VEH in the double-blind trials who were newly exposed to GT in the open-label extension

Safety

- Overall, GT was well tolerated, and most patients who experienced TEAEs had mild to moderate events; few discontinued due to TEAEs (**Table 3**)
- The most frequently reported TEAEs were dry mouth (16.9%), vision blurred (6.7%), and application site pain (6.4%)
- 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
  - TEAEs of special interest infrequently led to drug withdrawal, and most events were managed by dose interruption or no action and resolved within 3 to 14 days of onset
- The incidence of dry mouth decreased over time and was highest in the first 4 weeks of the open-label extension for patients who were newly exposed to GT in the open-label extension (ie, had received vehicle during the double-blind lead-in trials), though rates of drug withdrawal due to TEAEs were not higher in this patient population (**Table 4**)
- A reduction in adverse events over time may be due to several factors, including patient selection as those experiencing TEAEs discontinued, increased time length between visits, increased patient experience with drug application, and/or acclimation to adverse events

Table 3. Summary of Treatment-Emergent Adverse Events in ARIDO (Safety Population[a])

n (%)	GT→GT N=361	VEH→GT N=189	Total (N=550)
Any TEAE	210 (58.2)	119 (63.0)	329 (59.8)
Any Serious TEAE[b]	6 (1.7)	1 (0.5)	7 (1.3)
Discontinuation due to TEAE	26 (7.2)	17 (9.0)	43 (7.8)
Deaths	0	0	0
TEAEs by Severity Mild Moderate Severe	95 (26.3) 98 (27.1) 17 (4.7)	53 (28.0) 55 (29.1) 11 (5.8)	148 (26.9) 153 (27.8) 28 (5.1)
Relation to Study Drug Not related Related	90 (24.9) 120 (33.2)	41 (21.7) 78 (41.3)	131 (23.8) 198 (36.0)
Most frequently reported TEAEs (>5% patients) Dry mouth Vision blurred Application site pain Nasopharyngitis Mydriasis	47 (13.0) 21 (5.8) 27 (7.5) 24 (6.6) 21 (5.8)	46 (24.3) 16 (8.5) 8 (4.2) 8 (4.2) 8 (4.2)	93 (16.9) 37 (6.7) 35 (6.4) 32 (5.8) 29 (5.3)
AESIs (prespecified anticholinergic TEAEs of special interest) Vision blurred Mydriasis Urinary hesitation Nocturia Urine flow decreased Hypermetropia Pollakiuria Pupils unequal	51 (14.1) 21 (5.8) 21 (5.8) 13 (3.6) 2 (0.6) 1 (0.3) 1 (0.3) 1 (0.3) 1 (0.3)	27 (14.3) 16 (8.5) 8 (4.2) 10 (5.3) 0 1 (0.5) 0 0 0	78 (14.2) 37 (6.7)[c] 29 (5.3)[d] 23 (4.2) 2 (0.4) 2 (0.4) 1 (0.2) 1 (0.2) 1 (0.2)

[a]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
[b]Infectious colitis, affective disorder, suicide attempt, mydriasis, chest pain, concussion
[c]37 patients reported 45 vision blurred events; 40 (88.9%) were bilateral
[d]29 patients reported 37 mydriasis events; 31 (83.8%) were bilateral
Percentages in this table represent the number of patients reporting one or more TEAEs, not number of events; small discrepancies in overall totals reflect differences in source data (Adverse Event form vs End of Study form)
GT, Glycopyrronium tosylate; GT→GT, patients assigned to GT in the double-blind trials who continued on GT in the open-label extension; TEAE, treatment-emergent adverse event; VEH, vehicle; VEH→GT, patients assigned to VEH in the double-blind trials who were newly exposed to GT in the open-label extension

Table 4. Safety Outcomes Over Time in the Open-Label Extension According to Treatment

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	
	GT→GT n=361	VEH→GT n=189	GT→GT n=350	VEH→GT n=187	GT→GT n=313	VEH→GT n=166	GT→GT n=270	VEH→GT n=147	GT→GT n=237	VEH→GT n=128
Drug Withdrawn due to TEAE	16 (4.4)	5 (2.6)	12 (3.4)	2 (1.1)	11 (3.5)	1 (0.6)	3 (1.1)	0	1 (0.4)	0
TEAEs reported in ≥5% of patients										
Dry mouth	26 (7.2)	33 (17.5)	14 (4.0)	9 (4.8)	9 (2.9)	10 (6.0)	8 (3.0)	7 (4.8)	3 (1.3)	2 (1.6)
Vision blurred	8 (2.2)	3 (1.6)	7 (2.0)	7 (3.7)	3 (1.0)	4 (2.4)	2 (0.7)	3 (2.0)	3 (1.3)	1 (0.8)
Application site pain	11 (3.0)	5 (2.6)	7 (2.0)	2 (1.1)	4 (1.3)	1 (0.6)	6 (2.2)	0	3 (1.3)	0
Nasopharyngitis	9 (2.5)	5 (2.6)	8 (2.3)	1 (0.5)	3 (1.0)	1 (0.6)	5 (1.9)	0	2 (0.8)	1 (0.8)
Mydriasis	5 (1.4)	3 (1.6)	4 (1.1)	4 (2.1)	7 (2.2)	2 (1.2)	4 (1.5)	1 (0.7)	2 (0.8)	0

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
EOS, end of study; GT, Glycopyrronium tosylate; GT→GT, patients assigned to GT in the double-blind trials who continued on GT in the open-label extension; TEAE, treatment-emergent adverse event; VEH, vehicle; VEH→GT, patients assigned to VEH in the double-blind trials who were newly exposed to GT in the open-label extension

CONCLUSIONS

- Patients treated with GT showed reduced sweating severity and sweat production (coprimary endpoints) and improvements in quality of life assessments in two 4-week, vehicle-controlled, phase 3, double-blind trials compared with patients treated with vehicle
- In the open-label extension trial, improvements in efficacy were maintained through Week 44 irrespective of randomized treatment in the double-blind trials
  - Patients previously receiving GT in the double-blind trials maintained levels of HDSS response and cfB in DLQI that were similar to those observed in the double-blind trials
  - Patients newly exposed to GT in the open-label extension showed a marked response to GT observed as early as Week 2, as measured by HDSS response; this was similar to results observed for the GT arm of the double-blind trials
  - Similar results were observed for the DLQI, though the first DLQI assessment in the open-label trial occurred later (Week 20)
- The most common TEAE in the open-label extension, regardless of treatment in the double-blind phase, was dry mouth, which occurred most frequently in those newly exposed to GT during the first 4 weeks of the open-label extension
- GT, applied once-daily to both axillae, was generally well tolerated in patients with primary axillary hyperhidrosis over a maximum of 48 weeks in this open-label extension study

REFERENCES

1. Doolittle et al. *Arch Dermatol Res.* 2016;308(10):743-9.
2. QBREXZA™ (glycopyrronium) cloth [Prescribing Information]. Dermira, Inc., Menlo Park, CA. 2018.
3. Glaser DA, Hebert AA, Nast A, et al. Topical glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: Results from the ATMOS-1 and ATMOS-2 phase 3 randomized controlled trials. *J Am Acad Dermatol.* 2018 Jul 10. pii: S0190-9622(18)32224-2. doi:10.1016/j.jaad.2018.07.002. [Epub ahead of print].

ACKNOWLEDGEMENTS

This study was funded by Dermira, Inc. Medical writing support was provided by Prescott Medical Communications Group (Chicago, IL). All costs associated with development of this poster were funded by Dermira, Inc.

AUTHOR DISCLOSURES

ELL: Consultant for Dermira, Inc. **DG:** Consultant for Dermira, Inc., and an investigator for Allergan, Atacama Therapeutics, Brickell Biotech, Inc., Galderma, and Revance Therapeutics, Inc. She has received honoraria for consulting with Allergan and Dermira, Inc. **RG, VY, JD:** Employee of Dermira, Inc. **DMP:** Consultant and investigator for Dermira, Inc.

Poster presented at the 77th Annual Meeting of the American Academy of Dermatology; March 1-5, 2019; Washington, DC