Open-Label Study (ARIDO) Evaluating Long-Term Safety of Topical Glycopyrronium Tosylate (GT) in Patients With Primary Axillary Hyperhidrosis

Dee Anna Glaser,[1] Adelaide A. Hebert,[2] Alexander Nast,[3] William P. Werschler,[4] Stephen Shideler,[5] Lawrence Green,[6] Richard D. Mamelok,[7] Janice Drew,[8] John Quiring,[9] David M. Pariser[10]

[1]Saint Louis University, St. Louis, MO; [2]UTHealth McGovern Medical School, Houston, TX; [3]Charité–Universitätsmedizin Berlin, Berlin, Germany; [4]Premier Clinical Research, Spokane, WA; [5]Shideler Dermatology and Skin Care Center, Carmel, IN; [6]George Washington University School of Medicine, Washington, DC; [7]Mamelok Consulting, Palo Alto, CA; [8]Dermira, Inc., Menlo Park, CA; [9]QST Consultations, Allendale, MI; [10]Eastern Virginia Medical School and Virginia Clinical Research, Inc., Norfolk, VA

INTRODUCTION

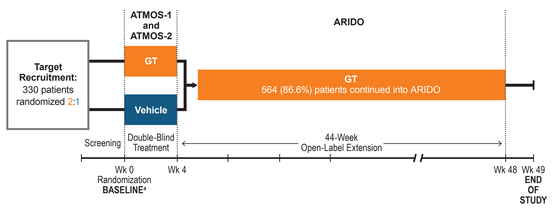
- Hyperhidrosis affects an estimated 4.8% of the US population or approximately 15.3 million people,[1] and the impact of hyperhidrosis on quality of life is reported as comparable to, or greater than, psoriasis or eczema[2]
- Topical glycopyrronium tosylate (GT; formerly DRM04) is a cholinergic receptor antagonist being developed for the treatment of primary axillary hyperhidrosis in patients ≥9 years of age
- GT has been assessed in 2 replicate, randomized, double-blind, vehicle-controlled, pivotal phase 3 lead-in trials (ATMOS-1 and ATMOS-2)
  - GT was generally well tolerated and demonstrated clinically meaningful improvements in disease severity and reductions in sweat production through 4 weeks in these trials[3]
- This 44-week, open-label extension study (ARIDO; NCT02553798) assessed the long-term safety of GT in patients with primary axillary hyperhidrosis who completed ATMOS-1 (NCT02530281; sites in the US and Germany) or ATMOS-2 (NCT02530294, sites in US only)

METHODS

Study Design

- ARIDO was a 44-week open-label extension of ATMOS-1/ATMOS-2, 4-week, double-blind, phase 3 clinical trials in which patients with primary axillary hyperhidrosis were randomized 2:1 to GT (3.75% topical solution) or vehicle applied once daily to each axilla for 28 days (**Figure 1**)
  - Patients who completed ATMOS-1/ATMOS-2 with ≥80% treatment compliance were eligible to continue into ARIDO and receive open-label GT for 44 weeks or to early termination (ET; **Figure 1**)
- Eligible patients were ≥9 years of age (patients <16 years were only recruited at US sites) and had primary axillary hyperhidrosis for ≥6 months, with gravimetrically-measured sweat production of ≥50 mg/5 min in each axilla, Axillary Sweating Daily Diary (ASDD; for patients ≥16 years of age) or ASDD-Children (ASDD-C; for patients <16 years of age) axillary sweating severity item (Item 2)[4] score ≥4 (0 to 10 numeric rating scale), and Hyperhidrosis Disease Severity Scale (HDSS) ≥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; 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; and/or conditions that could be exacerbated by study medication

Figure 1. Study Design



[a]Baseline for ARIDO was Week 0 of ATMOS-1/ATMOS-2
GT, topical glycopyrronium tosylate; Wk, week

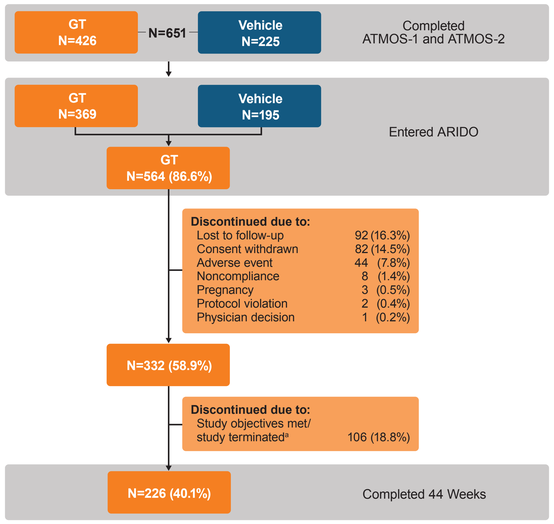
Assessments

- Primary objective was long-term safety
  - Safety was evaluated via treatment-emergent adverse events (TEAEs) through Week 45 (Week 44 + 1 week safety follow-up), local skin reactions (LSRs) through Week 44, laboratory testing, vital signs, and physical examinations
  - TEAEs are summarized overall from Baseline in ATMOS-1/ATMOS-2 to Week 45 (up to 48 weeks of GT) and by duration of exposure to GT in both ATMOS-1/ATMOS-2 and ARIDO
- Descriptive efficacy assessments evaluated in ARIDO were an extension of the primary endpoints in ATMOS-1/ATMOS-2
  - Change from Baseline in ATMOS-1/ATMOS-2 in gravimetrically-measured sweat production at Week 44 (up to 48 weeks of GT)
  - Change from Baseline in ATMOS-1/ATMOS-2 in HDSS responder rate (≥2-grade improvement) at Week 44 (up to 48 weeks of GT)
- All safety and efficacy analyses were performed on the Safety Population (patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO)

RESULTS

- The majority of patients (86.6%; N=564) completing ATMOS-1/ATMOS-2 (369 patients [65.4%] had received GT, and 195 [34.6%] had received vehicle) continued into ARIDO (**Figure 2**)
- Of the patients enrolled in ARIDO, most patients were female (55.3%) and white (83.3%) with a mean age of 33.0 years and mean BMI of 27.3 kg/m^2 (**Table 1**)
- The trial was terminated, per protocol, once study objectives were reached
  - A total of 226 patients completed 44 weeks of treatment

Figure 2. Patient Disposition



[a]Sponsor terminated study early, per protocol, when study objective of 100 patients receiving treatment for at least 12 months was achieved
GT, topical glycopyrronium tosylate

Table 1. Demographics and Baseline[a] Disease Characteristics (Safety Population[b])

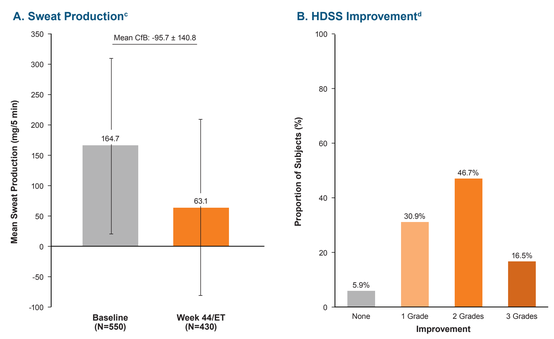
	GT (N=550)
Demographics	
Age (years), mean ± SD	33.0 ± 11.4
Age group, n (%)	
≥16 years	522 (94.9)
<16 years	28 (5.1)
Female, n (%)	304 (55.3)
White, n (%)	458 (83.3)
BMI (kg/m^2), mean ± SD	27.3 ± 5.0
Baseline Disease Characteristics	
Sweat production (mg/5 min),[c] mean ± SD	164.7 ± 145.0
HDSS,[d,e] n (%)	
Grade 3	348 (63.3)
Grade 4	201 (36.5)
Quality of Life	
DLQI,[f] mean ± SD	11.4 ± 5.9
CDLQI,[g] mean ± SD	8.9 ± 5.4

[a]Baseline in ATMOS-1/ATMOS-2
[b]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
[c]Gravimetrically-measured average from the left and right axillae
[d]HDSS ≥3 was an inclusion criteria
[e]N=549; 1 subject entered ATMOS-2 with HDSS=2, which was a protocol violation
[f]Patients ≥16 years of age
[g]Patients <16 years of age
BMI, body mass index; CDLQI, Children's DLQI; DLQI, Dermatology Life Quality Index; GT, topical glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; SD, standard deviation

Efficacy Assessments

- Through Week 44/ET in ARIDO (up to 48 weeks of GT), GT-treated patients continued to demonstrate improvements in efficacy measures, including sweat production and HDSS responder rate (**Figure 3**)
  - From Baseline in ATMOS-1/ATMOS-2 to Week 44/ET in ARIDO, mean sweat production decreased by 95.7 ± 140.8 mg/5 min, which was maintained from a decrease of 107.6 ± 207.2 mg/5 min in GT-treated patients after 4 weeks in ATMOS-1/ATMOS-2 (**Figure 3A**)
  - At Week 44/ET in ARIDO, HDSS responder rate (≥2-grade improvement) was 63.2%, a further improvement from 59.1% in GT-treated patients at Week 4 in ATMOS-1/ATMOS-2
    - HDSS grade improved by 1, 2, and 3 grades in 30.9%, 46.7%, and 16.5% of patients, respectively (**Figure 3B**)

Figure 3. Mean Sweat Production and HDSS Improvement From Baseline[a] to Week 44/ET (Safety Population[b])



[a]Baseline in ATMOS-1/ATMOS-2
[b]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
[c]Gravimetrically-measured average from the left and right axillae
[d]N=437
CfB, change from Baseline; ET, early termination; HDSS, Hyperhidrosis Disease Severity Scale

Safety Assessments

- After 48 weeks, 329 (59.8%) patients reported ≥1 TEAE, though most were mild or moderate in severity (**Table 2**)
- A total of 44 (8.0%) patients discontinued due to a TEAE and 7 (1.3%) reported ≥1 serious TEAE (**Table 2**)
- Prespecified anticholinergic TEAEs of interest were reported in 78 (14.2%) patients; most were mild or moderate in severity and were able to be managed by dose interruption (**Table 2**)
  - 37 patients reported 45 vision blurred events; 40 (88.9%) were bilateral
  - 29 patients reported 37 mydriasis events; 31 (83.8%) were unilateral
- Generally, TEAEs, including TEAEs prespecified as anticholinergic TEAEs of interest, did not increase over time with longer duration of exposure (**Table 3**)
- 179 (32.5%) of patients reported LSRs, which were typically mild or moderate in severity (**Figure 4**)
- There were no clinically meaningful changes in laboratory parameters or vital signs

Table 2. Summary of Treatment-Emergent Adverse Events From Baseline[a] to Week 45/ET (Safety Population[b])

	GT (N=550)
Any TEAE, n (%)	329 (59.8)
Any Serious TEAE, n (%)	7 (1.3)[c]
Discontinuation due to a TEAE, n (%)	44 (8.0)
Deaths, n (%)	0
Most frequently reported TEAEs (>5% patients), n (%)	
Dry mouth	93 (16.9)
Vision blurred	37 (6.7)
Application site pain	35 (6.4)
Nasopharyngitis	32 (5.8)
Mydriasis	29 (5.3)
Prespecified anticholinergic TEAEs of interest, n (%)	78 (14.2)
Vision blurred	37 (6.7)[d]
Mydriasis	29 (5.3)[e]
Urinary hesitation	23 (4.2)
Nocturia	2 (0.4)
Urine flow decreased	2 (0.4)
Hypermetropia	1 (0.2)
Pollakiuria	1 (0.2)
Pupils unequal	1 (0.2)
	Any TEAEs (N=329)
TEAEs by severity, n (%)	
Mild	148 (45.0)
Moderate	153 (46.5)
Severe	28 (8.5)
Relation to study drug, n (%)	
Not related	131 (39.8)
Related	198 (60.2)

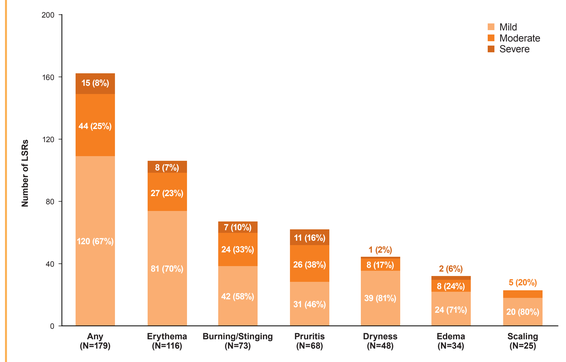
Numbers in table represent the number of patients reporting ≥1 TEAE, not number of events
[a]Baseline in ATMOS-1/-2
[b]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
[c]Infectious colitis, affective disorder, suicide attempt, mydriasis, chest pain, concussion, diverticulitis
[d]37 patients reported 45 vision blurred events; 40 (88.9%) were bilateral
[e]29 patients reported 37 mydriasis events; 31 (83.8%) were unilateral
ET, early termination; GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

Table 3. Summary of Frequently Reported TEAEs and TEAEs of Special Interest (Safety Population)[a,b]

TEAEs, n (%)	Duration of Exposure: 0 to 4 weeks (N=550)	>4 to 8 weeks (N=537)	>8 to 20 weeks (N=479)	>24 to 36 weeks (N=417)	>36 weeks to ES (N=365)
Any TEAE	176 (32.0)	148 (27.6)	102 (21.3)	78 (18.7)	59 (16.2)
TEAEs reported in >5% of patients					
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	8 (1.5)	8 (1.5)	9 (1.9)	5 (1.2)	2 (0.5)
Prespecified anticholinergic TEAEs of interest					
Vision blurred	11 (2.0)	14 (2.6)	7 (1.5)	5 (1.2)	4 (1.1)
Mydriasis	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	0	0	0	1 (0.2)	0
Pollakiuria	0	0	0	1 (0.2)	0
Pupils unequal	1 (0.2)	0	0	0	0

Numbers in table represent the number of patients reporting ≥ TEAE, not number of events
[a]In ATMOS-1/ATMOS-2 and ARIDO combined
[b]Patients receiving ≥1 dose of GT and having ≥1 post Baseline assessment on ARIDO
ES, end of study; GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

Figure 4. Summary of Local Skin Reactions by Severity From Baseline[a] to Week 44/ET (Safety Population[b])



Patients were counted as having an LSR if any post-Baseline assessment was mild, moderate, or severe
[a]Baseline in ATMOS-1/ATMOS-2
[b]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
GT, topical glycopyrronium tosylate; LSR, local skin reaction

CONCLUSIONS

- Safety results were consistent with anticholinergic treatment and with the safety profile observed in prior GT studies,[3] with no new or unexpected findings
  - Most TEAEs were mild or moderate in severity and considered by the Investigator to be related to study drug
  - A low number of subjects discontinued due to a TEAE
  - While approximately one-third of patients reported LSRs, most were mild or moderate in severity
  - Incidence of TEAEs, including prespecified anticholinergic TEAEs of interest, did not increase with long-term treatment
- Efficacy measures obtained at the end of treatment in ARIDO indicated that subjects had maintained sweat production reduction and less bothersome sweating compared with Baseline in ATMOS-1/ATMOS-2
- GT was generally well tolerated and improvements in efficacy measures were maintained in patients with primary axillary hyperhidrosis when applied once daily to both axillae over a maximum of 48 weeks

References

1. Doolittle et al. *Arch Dermatol Res.* 2016;308(10):743-9. **2.** Hamm. *Dermatol Clin.* 2014;32(4):467-76. **3.** Pariser et al. Poster presented at: 25th European Academy of Dermatology and Venerology Congress; September 28-October 2, 2016; Vienna, Austria. **4.** Glaser et al. Poster presented at: 13th Maui Derm for Dermatologists Congress; March 20-24, 2017; Maui, HI.

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

DAG: Consultant and investigator for Dermira, Inc. **AAH:** Consultant for Dermira, Inc.; employee of the University of Texas Medical School, Houston, which received compensation from Dermira, Inc. for study participation. **AN:** Employee of Charité – Universitätsmedizin Berlin, which received compensation from Dermira, Inc. for study participation. **WPW:** Consultant and investigator for Dermira, Inc. **SS:** Investigator for Dermira, Inc. **LG:** Consultant and investigator for Dermira, Inc.; investigator for Brickell. **RDM:** Consultant for Dermira, Inc. **JD:** Employee of Dermira, Inc. **JQ:** Employee of QST Consultations.**DMP:** Consultant and investigator for Dermira, Inc.

Poster presented at the 36th Fall Clinical Dermatology Conference | Las Vegas, NV | October 12-15, 2017