Topical Glycopyrronium Tosylate (DRM04) for the Treatment of Primary Axillary Hyperhidrosis: Pooled Results from the ATMOS-1 and ATMOS-2 Phase 3 Randomized Controlled Trials

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

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

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 experienced by approximately 75% of patients 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; formerly DRM04) is an investigational cholinergic receptor antagonist developed for topical application for the treatment of primary axillary hyperhidrosis
- GT has been assessed in two randomized, phase 3 clinical trials (ATMOS-1 and ATMOS-2); the primary efficacy and safety results of these studies have been previously reported[3]
- Patient-reported outcomes (PROs) in these trials were assessed using recently developed Axillary Hyperhidrosis Patient Measures (AHPM) which includes three separate assessments: the 4-item Axillary Sweating Daily Diary (ASDD; patients <16 years of age completed a modified, child-specific 2-item version [ASDD-C]), 6 Weekly Impact (WI) items, and a single-item Patient Global Impression of Change (PGIC)[3,4]
  - ASDD/ASDD-C axillary sweating severity item (Item 2) has been specifically developed and validated to support regulatory approval[3]

OBJECTIVE

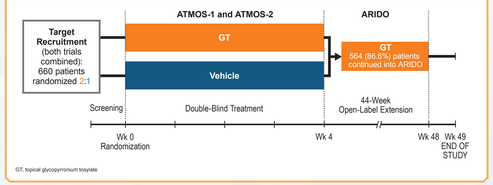
- To examine the efficacy and safety of GT treatment over 4 weeks using pooled results from ATMOS-1 and ATMOS-2

METHODS

ATMOS-1 and ATMOS-2 Study Design and Patients

- ATMOS-1 (DRM04-HH04; NCT02530281; sites in the US and Germany) and ATMOS-2 (DRM04-HH05; NCT02530294; US sites only) were parallel-group, 4-week, double-blind phase 3 clinical trials in which patients with primary axillary hyperhidrosis were randomized (2:1) to GT or vehicle[3] (**Figure 1**)
- 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, ASDD axillary sweating severity item (Item 2) ≥4, 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; 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. ATMOS-1/ATMOS-2 Study Design



GT, topical glycopyrronium tosylate

Efficacy and Safety Assessments

- Coprimary endpoints assessed at Week 4 were ASDD/ASDD-C Item 2 responder rate (≥4-point improvement from Baseline) and mean absolute change from Baseline (CfB) in gravimetrically-measured sweat production (average of both axillae)
- Secondary efficacy endpoints assessed at Week 4 were HDSS responder rate (≥2-grade improvement from Baseline) and sweat production responder rate (≥50% reduction from Baseline)
- Other efficacy endpoints assessed at Week 4 included CfB in Dermatology Life Quality Index (DLQI)/children's DLQI (CDLQI) and ASDD Items 3 and 4 (impact and bother of axillary sweating, respectively), as well as tabulation of Weekly Impact (WI) items
- Safety was assessed via treatment-emergent adverse events (TEAEs)
  - TEAEs of special interest were identified based on association with anticholinergic compounds and monitored during the study

Statistical Analysis

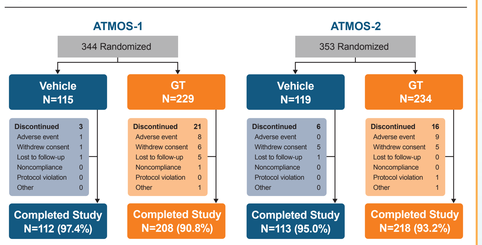
- Efficacy analyses were conducted for the intent-to-treat (ITT) population (all randomized subjects dispensed study drug) and safety analyses were conducted for the Safety Population (all randomized patients who received ≥1 confirmed dose of study drug)
  - Efficacy assessments in ATMOS-1 and ATMOS-2 at Week 4 were pre-specified and assessments at Weeks 1, 2 and 3 were post hoc
  - All pooled efficacy assessments were post hoc
- The Markov chain Monte Carlo method for multiple imputation was used for missing efficacy data
- ASDD/ASDD-C Item 2 responder rate was analyzed using the Cochran-Mantel-Haenszel test; CfB in sweat production and CfB in DLQI were each analyzed using an analysis of covariance (ANCOVA) model; responses to ASDD Items 3 and 4 were tabulated and there was no imputation for missing values

RESULTS

Disposition, Demographics, and Baseline Disease Characteristics

- 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 (**Figure 2**)
- Patient demographics and Baseline disease characteristics were similar across treatment arms and across studies (**Table 1**)

Figure 2. Patient Disposition



GT, topical glycopyrronium tosylate

Table 1. Patient Demographics and Baseline Disease Characteristics

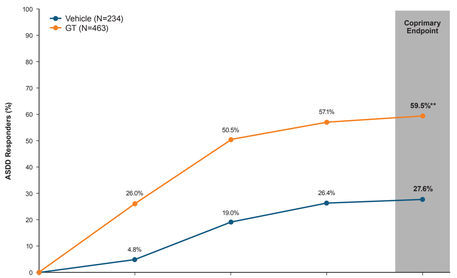
	ATMOS-1		ATMOS-2		Pooled	
	Vehicle (N=115)	GT (N=229)	Vehicle (N=119)	GT (N=234)	Vehicle (N=234)	GT (N=463)
Demographics						
Age (years), mean ± SD	34.0 ± 13.1	32.1 ± 11.2	32.8 ± 11.2	32.6 ± 10.9	33.4 ± 12.2	32.3 ± 11.0
Age group, n (%) ≥16 years	109 (94.8)	224 (97.8)	109 (91.6)	223 (95.3)	218 (93.2)	447 (96.5)
Male, n (%)	55 (47.8)	99 (43.2)	59 (49.6)	113 (48.3)	114 (48.7)	212 (45.8)
White, n (%)	94 (81.7)	182 (79.5)	102 (85.7)	192 (82.1)	196 (83.8)	374 (80.8)
Baseline Disease Characteristics						
Sweat production (mg/5 min), mean ± SD	170.3 ± 164.2	182.9 ± 266.9	181.9 ± 160.1	162.3 ± 149.5	176.2 ± 161.9	172.5 ± 215.7
ASDD Item 2 (sweating severity), mean ± SD	7.1 ± 1.7	7.3 ± 1.6	7.2 ± 1.6	7.3 ± 1.6	7.2 ± 1.6	7.3 ± 1.6
HDSS, n (%) Grade 3 Grade 4	84 (73.0) 31 (27.0)	133 (58.1) 96 (41.9)	71 (59.7) 47 (39.5)	144 (61.5) 90 (38.5)	155 (66.2) 78 (33.3)	277 (59.8) 186 (40.2)
DLQI (for patients >16 years of age), mean ± SD	10.1 ± 5.9	12.1 ± 6.5	11.2 ± 5.8	11.6 ± 5.7	10.6 ± 5.9	11.9 ± 6.1
CDLQI (for patients ≤16 years of age), mean ± SD [ATMOS-1: n=15; ATMOS-2: n=28]	6.9 ± 3.3	8.5 ± 6.5	9.5 ± 6.5	10.6 ± 5.1	8.5 ± 5.6	9.9 ± 5.5

ASDD, Axillary Sweating Daily Diary; BMI, body mass index; CDLQI, children's DLQI; DLQI, Dermatology Life Quality Index; GT, topical glycopyrronium tosylate; HDSS: Hyperhidrosis Disease Severity Scale; ITT, intent-to-treat; SD: standard deviation

Pooled Efficacy Endpoints

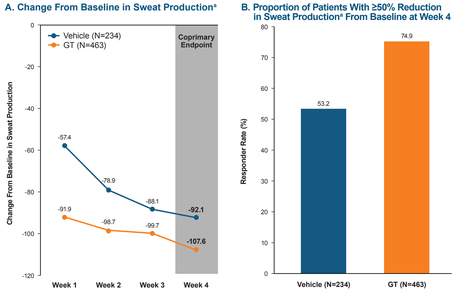
- More GT-treated patients achieved an ASDD Item 2 response (≥4-point improvement) compared with vehicle at Week 1 (26.0% vs 4.8%), Week 2 (50.5% vs 19.0%), Week 3 (57.1% vs 26.4%), and Week 4 (59.5% vs 27.6%; p<0.001) (**Figure 3**)
- Greater reductions in sweat production from Baseline were seen in GT- versus vehicle-treated patients at Week 1 (-91.9 mg vs -57.4 mg), Week 2 (-98.7 mg vs -78.9 mg), Week 3 (-99.7 mg vs -88.1 mg), and Week 4 (-107.6 mg vs -92.1 mg) (**Figure 4A**)
- More GT-treated patients had ≥50% reduction in gravimetrically-measured sweat production from Baseline at Week 4 compared with vehicle-treated patients (74.9% vs 53.2%; **Figure 4B**)

Figure 3. ASDD Item 2 Response Rate (≥4-Point Improvement)



ITT population; MCMC used to impute missing values. Summary statistics for Weeks 1, 2, 3 and 4 represent weighted average values
ASDD, Axillary Sweating Daily Diary; GT, topical glycopyrronium tosylate; ITT, intent-to-treat; MCMC, Markov chain Monte Carlo

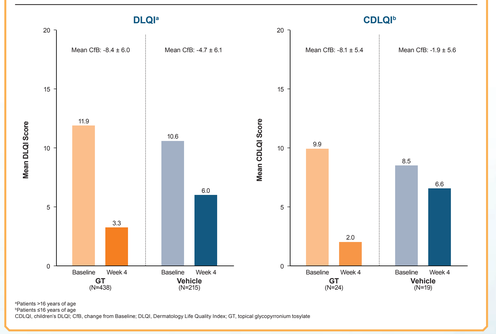
Figure 4. Sweat Production



*Gravimetrically-measured, average of both axillae
ITT population; MCMC used to impute missing values. Summary statistics for Weeks 1, 2, 3 and 4 in Panel A represent weighted average values
GT, topical glycopyrronium tosylate; ITT intent-to-treat; MCMC, Markov-chain Monte Carlo

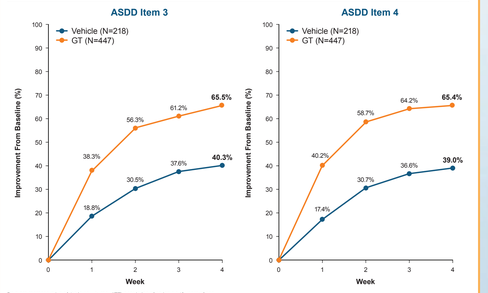
- GT-treated patients experienced greater reductions from Baseline in mean DLQI/CDLQI score at Week 4 compared with their vehicle-treated counterparts (DLQI, mean [SD]: -8.4 [6.0] vs -4.7 [6.1]; CDLQI: -8.1 [5.4] vs -1.9 [5.6]; **Figure 5**)
- There was greater improvement from Baseline at Week 4 in ASDD Item 3 (impact of axillary sweating) and Item 4 (bother of axillary sweating) in GT-treated patients compared with vehicle-treated patients (**Figure 6**)
- At Week 4 for WI items, the proportion of patients negatively impacted by aspects of sweating decreased from Baseline regardless of treatment, with greater reductions observed in GT- versus vehicle-treated patients (**Figure 7**)
- A higher proportion of GT-treated patients had ≥2-grade improvement in HDSS from Baseline at Week 4 compared with vehicle-treated patients (59.1% vs 25.7%)

Figure 5. Mean DLQI/CDLQI Score at Baseline and Week 4



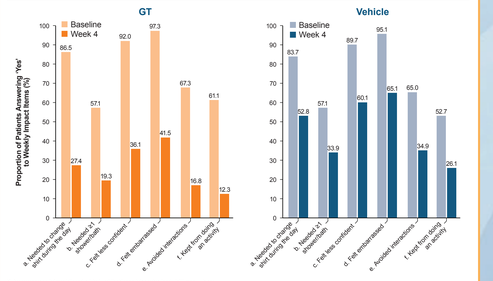
[a]Patients >16 years of age
[b]Patients ≤16 years of age
CDLQI, children's DLQI; CfB, change from Baseline; DLQI, Dermatology Life Quality Index; GT, topical glycopyrronium tosylate

Figure 6. ASDD Item 3 (Impact) and Item 4 (Bother) Improvement in Mean Score From Baseline to Week 4



Data are representative of the intent-to-treat (ITT) population of patients ≥16 years of age
ASDD Item 3: During the past 24 hours, to what extent did your underarm sweating impact your activities? (0=Not at all; 4=An extreme amount)
ASDD Item 4: During the past 24 hours, how bothered were you by your underarm sweating? (0=Not at all bothered; 4=Extremely bothered)
ASDD, Axillary Sweating Daily Diary; GT, topical glycopyrronium tosylate

Figure 7. Proportion of Patients Answering 'Yes' to Weekly Impact Items



Data are representative of the intent-to-treat (ITT) population of patients ≥16 years of age
GT, topical glycopyrronium tosylate

Safety

- The majority of TEAEs were mild or moderate, transitory, and infrequently led to discontinuation (**Table 2**)
- Two serious TEAEs were reported in GT-treated patients (moderate unilateral mydriasis [considered by the Investigator to be related to treatment]; moderate dehydration [considered by the Investigator to be unrelated to treatment]) (**Table 2**)
- The majority of TEAEs reported in the GT group were related to anticholinergic activity, and the most frequently reported anticholinergic TEAEs in GT-treated patients were dry mouth (24.2%), mydriasis (6.8%), and urinary hesitation (3.5%) (**Table 2**)

Table 2. Safety Overview (Safety Population)

	ATMOS-1		ATMOS-2		Pooled	
	Vehicle (N=114)	GT (N=227)	Vehicle (N=118)	GT (N=232)	Vehicle (N=232)	GT (N=459)
TEAEs, n (%)						
Any	33 (28.9)	123 (54.2)	42 (35.6)	134 (57.8)	75 (32.3)	257 (56.0)
Drug-related	18 (15.8)	77 (33.9)	20 (16.9)	102 (44.0)	38 (16.4)	179 (39.0)
Serious[a]	0	1 (0.4)	0	1 (0.4)	0	2 (0.4)
D/C due to TEAE, n (%)	1 (0.9)	8 (3.5)	0	9 (3.9)	1 (0.4)	17 (3.7)
Deaths, n (%)	0	0	0	0	0	0
TEAEs by intensity, n (%)						
Mild	22 (19.3)	79 (34.8)	31 (26.3)	91 (39.2)	53 (22.8)	170 (37.0)
Moderate	11 (9.6)	43 (18.9)	11 (9.3)	40 (17.2)	22 (9.5)	83 (18.1)
Severe	0	1 (0.4)	0	3 (1.3)	0	4 (0.9)
Anticholinergic TEAEs reported in >2% of patients,[b] n (%)						
Dry mouth	4 (3.5)	43 (18.9)	9 (7.6)	68 (29.3)	13 (5.6)	111 (24.2)
Mydriasis	0	15 (6.6)	0	16 (6.9)	0	31 (6.8)
Urinary hesitation	0	5 (2.2)	0	11 (4.7)	0	16 (3.5)
Dry eye	0	2 (0.9)	1 (0.8)	9 (3.9)	1 (0.4)	11 (2.4)
Vision blurred	0	8 (3.5)	0	8 (3.4)	0	16 (3.5)
Nasal dryness	1 (0.9)	5 (2.2)	0	7 (3.0)	1 (0.4)	12 (2.6)
Constipation	0	4 (1.8)	0	5 (2.2)	0	9 (2.0)
Urinary retention	0	1 (0.4)	0	6 (2.6)	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] >2% in any individual treatment arm in ATMOS-1 or ATMOS-2
D/C, discontinuation; GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

CONCLUSIONS

- Patients treated with topical GT showed clinically meaningful improvements in disease severity and reductions in sweat production at Week 4 compared with patients treated with vehicle
  - Improvements in gravimetrically-measured sweat production and ASDD Item 2 responder rates were seen as early as Week 1
  - Daily GT treatment over 4 weeks was generally well tolerated in patients ≥9 years of age with primary axillary hyperhidrosis

References

1. Doolittle et al. *Arch Dermatol Res.* 2016; 308 (10):743-9. 2. Spalding et al. *Value Health.* 2003;6(3):242. 3. Pariser et al. Poster presented at 13th Annual Maui Derm for Dermatologists; 2017; Maui, HI. 4. Nelson et al. Development and validation of the Axillary Sweating Daily Diary: A patient-reported outcome measure to assess sweating severity. *Br J Dermatol.* [Submitted]

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Disclosures

DMP: 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. **SS:** Investigator for Dermira, Inc. **LG:** Investigator for Brickell; Advisory Board member and investigator for Dermira. **RDM:** Consultant for Dermira, Inc. **JQ:** Employee of QST Consultations. **JD:** Employee of Dermira, Inc. **DAG:** Consultant and Investigator for Dermira, Inc.

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