Topical Glycopyrronium Tosylate Improves Axillary Hyperhidrosis Across a Broad Spectrum of Patients: Post Hoc Analyses of the ATMOS-1 and ATMOS-2 Phase 3 Randomized Controlled Trials in Patient Subpopulations

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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]
- It is unknown whether Baseline demographics or Baseline disease characteristics affect efficacy of GT

OBJECTIVE

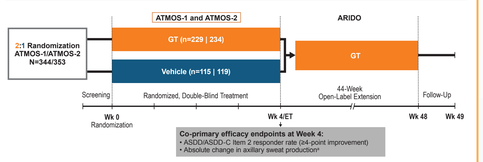
To evaluate the potential impact of patient Baseline disease characteristics and demographics on GT efficacy and safety, including hyperhidrosis focality, prior hyperhidrosis treatment, gender, age, race, and BMI across multiple outcomes

METHODS

Study Design

- Patients 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**)
- Eligible patients 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)/ ASSD-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

Figure 1. Study Design



*Gravimetrically measured
The ASDD/ASDD-C Item 2 is a numeric rating scale (0 to 10) for assessing axillary sweating severity that has demonstrated validity, reliability and responsiveness to axillary hyperhidrosis treatment effect in clinical trials[4]
ASDD, Axillary Sweating Daily Diary; ASDD-C, Axillary Sweating Daily Diary-Children (ages ≥9 to <16); ET, end of treatment for ATMOS-1 and ATMOS-2; GT, Glycopyrronium tosylate; Wk, week

Efficacy and Safety Assessments

- Co-primary endpoints assessed at Week 4 were
  - Axillary Sweating Daily Diary (ASDD) and child-specific ASDD (ASDD-C) Item 2 response (≥4-point improvement from Baseline in sweating severity)
  - Absolute change from Baseline in axillary sweat production (gravimetrically measured)
- Secondary efficacy endpoints assessed at Week 4 were
  - HDSS responder rate (≥2-grade improvement from Baseline)
  - Gravimetrically measured sweat production responder rate (≥50% reduction from Baseline; "Grav-50")
  - Dermatology Life Quality Index (DLQI) change from Baseline (cfB)
- Safety was assessed via treatment-emergent adverse events (TEAEs)

Analyses

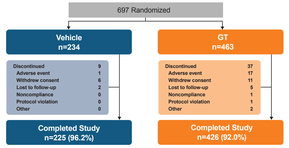
- ASDD/ASDD-C Item 2 response (≥4-point improvement), Grav-50 (≥50% sweat reduction), HDSS response (≥2-point improvement), DLQI mean cfB, and TEAEs were analyzed post hoc by:
  - Baseline disease characteristics: hyperhidrosis focality (multifocal: axillary only), prior hyperhidrosis treatment (no prior treatment: prior treatment [BOTOX, iontophoresis, miraDry, oral anticholinergics, topical anticholinergics, and others including over the counter and prescription antiperspirants])
  - Baseline demographics: gender (female: male), age (≤16y: >16y), race (non-white: white), and body mass index (BMI<25: BMI 25 to<30: BMI ≥ 30)
- Differences between GT and VEH in the proportion of responders (ASDD/ASDD-C Item 2, Grav-50, and HDSS) and cfB for DLQI with 95% confidence intervals (CI) were evaluated at Week 4
- Subpopulations were not controlled for in the study design
- 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)
- Markov chain Monte Carlo (MCMC) method for multiple imputation was used for missing efficacy data in the calculation of scores at Week 4, with the exception of DLQI, in which there was no imputation for missing data
- For the co-primary endpoints, statistical comparison between GT and VEH was prespecified for Week 4, and ASDD/ASDD-C Item 2 responder rate was analyzed using the Cochran-Mantel-Haenszel (CMH) test
- A sensitivity analysis was prespecified for primary endpoints to allow for identification of analysis centers with outlier data
  - Aforementioned analyses were analyzed both including and excluding 4 non-white outlier patients with extreme values for cfB in gravimetric sweat production at Week 4

RESULTS

Disposition, Baseline Disease Characteristics, and Subpopulations

- In the pooled population, 463 patients were randomized to GT and 234 to vehicle; 426 (92.0%) and 225 (96.2%) completed the trials, respectively (**Figure 2**)
- Patient Baseline disease characteristics were similar across treatment arms and across studies (**Table 1**)
- Sample sizes within subpopulations (**Table 2**) were similar when stratified by
  - Hyperhidrosis focality (multifocal: axillary only; n=346: 351)
  - Gender (female: male; n= 371: 326)
  - BMI (BMI <25: BMI 25 to <30: BMI ≥30; n=233: 271: 193)
- However, sample sizes varied when stratified by
  - Prior treatment (no prior treatment: prior treatment; n=522: 175)
  - Age (≤16y: >16y; n=44: 653)
  - Race (non-white: white; n=127: 570)

Figure 2. Patient Disposition



GT, Glycopyrronium tosylate

Table 1. Patient Baseline Disease Characteristics

	ATMOS-1 and ATMOS-2 Pooled	
	Vehicle N=234	GT N=463
Sweat production (mg/5 min), mean ± SD	176.2 ± 161.9	172.5 ± 215.7
ASDD/ASDD-C Item 2 (sweating severity), mean ± SD	7.2 ± 1.6	7.3 ± 1.6
HDSS, n (%)		
Grade 3	155 (66.2)	277 (59.8)
Grade 4	78 (33.3)	186 (40.2)
DLQI (for patients ≥16 years of age), mean ± SD	10.6 ± 5.9	11.9 ± 6.1
CDLQI (for patients <16 years of age), mean ± SD [ATMOS-1: n=11; ATMOS-2: n=21]	8.5 ± 5.6	9.9 ± 5.5

Intent-to-treat (ITT) population (Pooled). The ASDD/ASDD-C Item 2 is a numeric rating scale (0 to 10) for assessing axillary sweating severity that has demonstrated validity, reliability and responsiveness to axillary hyperhidrosis treatment effect in clinical trials[4]
ASDD, Axillary Sweating Daily Diary; ASDD-C, Axillary Sweating Daily Diary-Children (ages ≥9 to <16); CDLQI, children's DLQI; DLQI, Dermatology Life Quality Index; GT, Glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; SD, standard deviation

Table 2. Patient Baseline Demographics by Treatment Arm (Hyperhidrosis Focality, Prior Treatment, Gender, Age, Race, and BMI at Baseline)

	Vehicle N=234	GT N=463	Total N=697
HH Focality,* n (%)			
Multifocal	113 (48.3)	233 (50.3)	346 (49.6)
Palmar	73 (31.2)	167 (36.1)	240 (34.4)
Plantar	61 (26.1)	143 (30.9)	204 (29.3)
Face	31 (13.2)	54 (11.7)	85 (12.2)
Scalp	24 (10.3)	52 (11.2)	76 (10.9)
Trunk	38 (16.2)	70 (15.1)	108 (15.5)
None (Axillary Only)	121 (51.7)	230 (49.7)	351 (50.4)
Prior Treatment,* n (%)			
No Prior Treatment	177 (75.6)	345 (74.5)	522 (74.9)
Prior Treatment	57 (24.4)	118 (25.5)	175 (25.1)
BOTOX/Botulinum toxin	10 (4.3)	27 (5.8)	37 (5.3)
Iontophoresis	3 (1.3)	3 (0.6)	6 (0.9)
miraDry	0	0	0
Oral Anticholinergics	11 (4.7)	19 (4.1)	30 (4.3)
Topical Anticholinergics	14 (6.0)	18 (3.9)	32 (4.6)
Other	28 (12.0)	68 (14.7)	96 (13.8)
Sex, n (%)			
Female	120 (51.3)	251 (54.2)	371 (53.2)
Male	114 (48.7)	212 (45.8)	326 (46.8)
Age, n (%)			
≤16 years	19 (8.1)	25 (5.4)	44 (6.3)
>16 years	215 (91.9)	438 (94.6)	653 (93.7)
Race, n (%)			
Non-White	38 (16.2)	89 (19.2)	127 (18.2)
Black/African American	30 (12.8)	59 (12.7)	89 (12.8)
Asian	0	5 (1.1)	5 (0.7)
American Indian /Alaska Native	0	4 (0.9)	4 (0.6)
Native Hawaiian or Other Pacific Islander	2 (0.9)	0	2 (0.3)
Other	6 (2.6)	21 (4.5)	27 (3.9)
White	196 (83.8)	374 (80.8)	570 (81.8)
BMI, n (%)			
<25	68 (29.1)	165 (35.6)	233 (33.4)
25 to <30	97 (41.5)	174 (37.6)	271 (38.9)
≥30	69 (29.5)	124 (26.8)	193 (27.7)

*Patients could be counted in more than one multi focal category and type of prior treatment
Intent-to-treat (ITT) population (Pooled)
BMI, body mass index; HH, hyperhidrosis; GT, Glycopyrronium tosylate

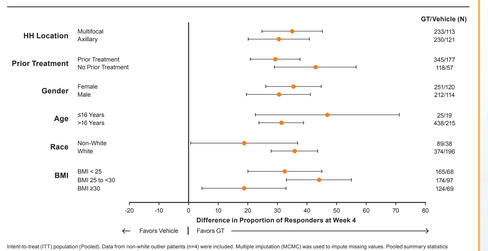
Efficacy: Co-Primary Endpoints

- In the pooled population, GT (n=463) demonstrated a significant advantage over VEH (n=234) on both co-primary endpoints (*P*<0.001; ASDD/ASDD-C Item 2 response and absolute change in sweat production)[3]

Efficacy: Subpopulation Findings (ASDD/ASDD-C Item 2, Grav-50, HDSS, and DLQI)

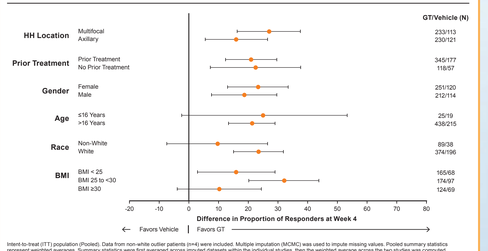
- Differences between GT and VEH showed that GT was numerically superior to VEH for all measurements (ASDD/ASDD-C Item 2 response, Grav-50, HDSS response, and DLQI mean cfB) across all subpopulations, with more variability and a wider range of the 95% CI within the race and age subgroups (**Figure 3-6**)
  - For patients who were ≤16y, non-white, and with BMI ≥30, the small sample size, wide range of the 95% CI, and lack of adjustment for Baseline differences for these subpopulations may underlie the observed results in those subpopulations
- Similar results were observed when 4 non-white outlier patients (ie, identified via prespecified sensitivity analysis of gravimetric sweat production data) were excluded from the analyses (data not shown)
- Specifically, GT remained superior to VEH for all measures, however 95% confidence intervals of HDSS responder rate overlapped between white and non-white subcategories when outliers were excluded, as opposed to non-overlap when outliers were included (**Figure 5**)

Figure 3. ASDD/ASDD-C Item 2 Responder Rate (≥4-Point Improvement) at Week 4



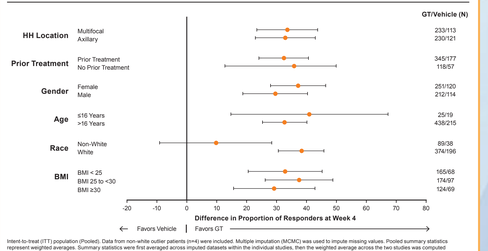
Intent-to-treat (ITT) population (Pooled). Data from non-white outlier patients (n=4) were included. Multiple imputation (MCMC) was used to impute missing values. Pooled summary statistics represent weighted averages. Summary statistics were first averaged across imputed datasets within the individual studies, then the weighted average across the two studies was computed.
The ASDD/ASDD-C Item 2 is a numeric rating scale (0 to 10) for assessing axillary sweating severity that has demonstrated validity, reliability and responsiveness to axillary hyperhidrosis treatment effect in clinical trials[4]
ASDD, Axillary Sweating Daily Diary; ASDD-C, Axillary Sweating Daily Diary-Children (ages ≥9 to <16); BMI, body mass index; GT, Glycopyrronium tosylate; HH, hyperhidrosis

Figure 4. Grav-50 Responder Rate (≥50% Reduction) at Week 4



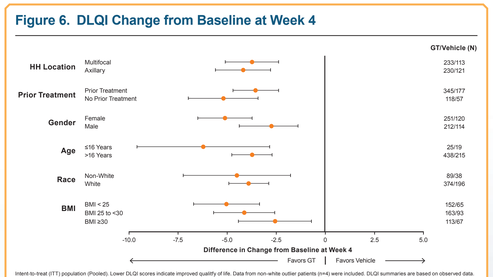
Intent-to-treat (ITT) population (Pooled). Data from non-white outlier patients (n=4) were included. Multiple imputation (MCMC) was used to impute missing values. Pooled summary statistics represent weighted averages. Summary statistics were first averaged across imputed datasets within the individual studies, then the weighted average across the two studies was computed
The average of the right and left axillae is used for gravimetrically measured sweat.
BMI, body mass index; GT, Glycopyrronium tosylate; HH, hyperhidrosis

Figure 5. HDSS Responder Rate (≥2-Point Improvement) at Week 4



Intent-to-treat (ITT) population (Pooled). Data from non-white outlier patients (n=4) were included. Multiple imputation (MCMC) was used to impute missing values. Pooled summary statistics represent weighted averages. Summary statistics were first averaged across imputed datasets within the individual studies, then the weighted average across the two studies was computed
BMI, body mass index; GT, Glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; HH, hyperhidrosis

Figure 6. DLQI Change from Baseline at Week 4



Intent-to-treat (ITT) population (Pooled). Lower DLQI scores indicate improved quality of life. Data from non-white outlier patients (n=4) were included. DLQI summaries are based on observed data. Pooled summary statistics represent weighted averages. Summary statistics were first averaged across imputed datasets within the individual studies, then the weighted average across the two studies was computed.
BMI, body mass index; DLQI, Dermatology Life Quality Index; GT, Glycopyrronium tosylate; HH, hyperhidrosis

Safety

- Overall, GT was well tolerated, and most adverse events were mild to moderate in severity and infrequently led to discontinuation
- 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%)
- Differences in the incidence of TEAEs between subgroups were analyzed descriptively; limitations in interpreting these data include small sample sizes of the non-white and the ≤ 16 year patient subgroups
- The incidence of anticholinergic TEAEs that occurred at a difference >5% between subgroups for GT-treated patients were (% [n/N]):
  - Dry mouth
    - Males vs females (30.5% [64/210] vs 18.9% [47/249])
    - White vs non-white patients (27.0% [100/371] vs 12.5% [11/88])
    - Multifocal vs axillary alone (27.3% [63/231] vs 21.1% [48/228])
    - BMI <25 vs 25 to <30 vs ≥30 (17.9% [29/162] vs 28.3% [49/173] vs 26.6% [33/124])
  - Mydriasis
    - Patients ≤16 vs >16 years (16.0% [4/25] vs 6.2% [27/434])
    - BMI <25 vs ≥30 (9.3% [15/162] vs 4.0% [5/124])
  - Vision blurred
    - Patients ≤16 vs >16 years (12.0% [3/25] vs 3.0% [13/434])
  - Urinary hesitation
    - Males vs females (6.7% [14/210] vs 0.8% [2/249])

CONCLUSIONS

- In this post hoc analysis of phase 3 trials in patients with primary axillary hyperhidrosis
  - GT applied topically once-daily reduced sweating severity (ASDD Item 2) and sweat production (Grav-50), and improved two quality of life measures (HDSS, DLQI) compared with VEH across a broad spectrum of patients
  - Daily GT treatment over 4 weeks was generally well tolerated in patients ≥9 years of age; in GT-treated patients, anticholinergic TEAEs of dry mouth, mydriasis, vision blurred, and urinary hesitation occurred at different incidences in certain patient subgroups
  - The availability of topical, once-daily GT provides a noninvasive, effective treatment option for primary axillary hyperhidrosis regardless of patient characteristics, including hyperhidrosis focality, prior hyperhidrosis treatment, gender, age, race, and BMI

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AUTHOR DISCLOSURES

DG: Consultant for Dermira, Inc., and an investigator for Allergan; Alacarna Therapeutics, Brickell Biotech, Inc., Galderma, and Revance Therapeutics, Inc. She has received honoraria for consulting with Allergan and Dermira, Inc. **LG:** Investigator for Brickell; Advisory Board member and investigator for Dermira. **JD, RG, MZ:** Employee of Dermira, Inc. **DMP:** Consultant and investigator for Dermira, Inc.

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