Short- and Long-Term Efficacy and Safety of Glycopyrronium Cloth for the Treatment of Primary Axillary Hyperhidrosis: Post Hoc Pediatric Subgroup Analyses from the Phase 3 Studies

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INTRODUCTION

- Hyperhidrosis, a 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]
  - In an online survey, 17.1% of US teens reported experiencing excessive sweating[2]
- Hyperhidrosis is largely undertreated and underdiagnosed, particularly among pediatric patients[1-3,4]
- Glycopyrronium tosylate (GT) is a topical anticholinergic recently approved by the US Food and Drug Administration for primary axillary hyperhidrosis in patients ≥9 years of age (glycopyrronium cloth, 2.4%, for topical use)[5]
- GT improved disease severity, reduced sweat production, and improved quality of life in patients evaluated in two randomized, double-blind Phase 3 studies for primary axillary hyperhidrosis (ATMOS-1 [NCT02530281] and ATMOS-2 [NCT02530294]), and in the open-label study (ARIDO [NCT02553789])[6-8]
- ATMOS-1 and ATMOS-2 were the first randomized, controlled Phase 3 trials in primary axillary hyperhidrosis to enroll pediatric patients

OBJECTIVE

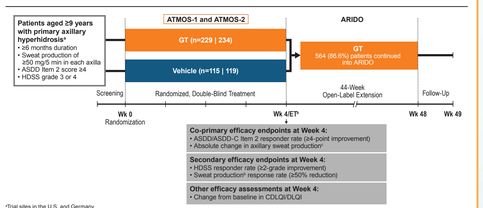
- Evaluate the short- and long-term efficacy of GT in pediatric patients (≥9 to ≤16 years) versus the older subgroup (>16 years) in a pooled post hoc analysis

METHODS

Study Design and Patients

- ATMOS-1 (NCT02530281; sites in the US and Germany) and ATMOS-2 (NCT02530294; US sites only) were parallel-group, 4-week, double-blind, Phase 3 clinical trials
  - Patients were randomized 2:1 to GT or VEH once daily (**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) sweating severity (Item 2) score ≥4, and Hyperhidrosis Disease Severity Scale (HDSS) ≥3
- ARIDO was a 44-week, open-label extension of ATMOS-1 (NCT02530281) and ATMOS-2 (NCT02530294)
  - Patients who completed ATMOS-1/ATMOS-2 with ≥80% treatment compliance were eligible to continue into ARIDO and receive open-label GT for up to 44 additional weeks or until early termination (study terminated once the study objective of 100 patients receiving treatment for ≥12 months was achieved; **Figure 1**)

Figure 1. ATMOS-1/ATMOS-2 and ARIDO Study Design



*Trial sites in the U.S. and Germany
†End of treatment for ATMOS-1 and ATMOS-2
‡Gravimetrically-measured
ASDD, Axillary Sweating Daily Diary; ASDD-C, ASDD-Children; CDLQI, children's DLQI; DLQI, Dermatology Life Quality Index; GT, topical glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; Wk, week

Assessments

- For the double-blind trials, coprimary efficacy endpoints were ASDD Item 2 (sweating severity) responder rate (≥4-point improvement from Baseline), a newly developed patient-reported outcome,[9] and absolute change from Baseline in axillary gravimetric sweat production at Week 4
  - A child-specific version of the ASDD (ASDD-C) was utilized for patients ≥9 to <16 years
  - 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]
- For the open-label extension, the primary outcome was evaluation of long-term safety
  - Safety was evaluated via treatment-emergent adverse events (TEAEs) through Week 45 (Week 44 + 1-week safety follow-up) and local skin reactions (LSRs) through Week 44
  - TEAEs are summarized from the first application of study drug in ARIDO to Week 45
  - Descriptive efficacy assessments were evaluated in ARIDO at Week 44 and relative to Baseline of ATMOS-1/ATMOS-2 (up to 48 weeks of GT) and were an extension of select ATMOS-1/ATMOS-2 endpoints
    - Gravimetrically-measured sweat production
    - HDSS responder rate (≥2-grade improvement)
    - Dermatology Life Quality Index (DLQI; patients >16 years) and children's DLQI (CDLQI; patients ≤16 years)

Analyses

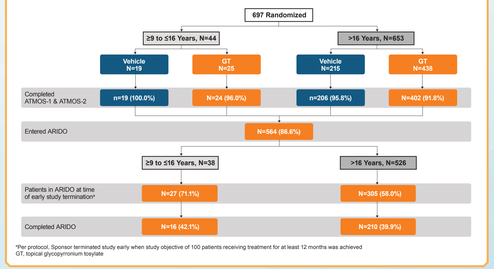
- This post hoc analysis evaluated pooled efficacy data according to patient age subgroups based on the DLQI and CDLQI, which have rigid age cutoffs for questionnaire administration
  - As such, the pediatric subgroup was defined to include patients ≥9 to ≤16 years and the older subgroup included patients >16 years
  - All efficacy and safety assessments were made in accordance with these subgroup definitions
  - As ASDD/ASDD-C Item 2 was psychometrically evaluated and validated, the standard age cutoffs (ASDD, ≥16 years; ASDD-C <16 years) for questionnaire administration could be and were modified to match the subgroup definitions established by the DLQI/CDLQI
- Data for each age group were evaluated as follows:
  - Short-term (Week 4)
    - ASDD/ASDD-C Item 2 responder rate (≥4-point improvement from Baseline)
    - Median absolute change from Baseline in gravimetrically-measured sweat production
    - HDSS responder rate (≥2-grade improvement from Baseline)
    - Mean change from Baseline in Dermatology Life Quality Index (DLQI) and children's DLQI (CDLQI)
  - Long-term (Week 44/End of Treatment [ET])
    - Median absolute change from Baseline in gravimetrically-measured sweat production
    - HDSS responder rate (≥2-grade improvement from Baseline)
    - Mean change from Baseline in Dermatology Life Quality Index (DLQI) and children's DLQI (CDLQI)
- In the evaluation of the double-blind data:
  - All efficacy analyses were conducted on the intent-to-treat (ITT) population (all patients who were randomized and dispensed study drug)
    - 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; change from Baseline in sweat production and change from Baseline in DLQI were each analyzed using an analysis of covariance (ANCOVA) model and there was no imputation for missing values; no imputation was made for missing DLQI and CDLQI data
  - Safety analyses were conducted on the safety population (all randomized patients who received ≥1 confirmed dose of study drug); no imputation was made for missing safety data
- For the long-term open-label extension study, safety and efficacy analyses were performed on the Safety Population (patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO)
- Statistical comparisons were not performed as the analysis was post hoc and not designed or powered to detect differences in the pediatric population

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**)
- Demographics and Baseline disease characteristics were generally well matched among treatment arms and between the pediatric and older subgroups (**Table 1**)
  - Ages of the pediatric and older subgroup patients ranged from 9-16 and 17-76, respectively
  - Although the older subgroup had greater gravimetrically-measured sweat production at Baseline, the standard deviations were large across all treatment groups for this assessment
- A total of 564/651 (86.6%) who completed ATMOS-1/ATMOS-2 entered ARIDO, 226/564 (40.1%) completed Week 44, and 550 comprised the analysis population

Figure 2. Patient Disposition



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

Table 1. Patient Demographics and Baseline Disease Characteristics (Baseline of Double-Blind Trials)

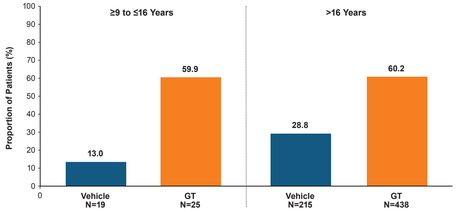
	≥9 to ≤16 Years		>16 Years	
	Vehicle N=19	GT N=25	Vehicle N=215	GT N=438
Demographics				
Age (years)				
Mean ± SD	14.1 ± 1.7	14.6 ± 1.4	35.1 ± 11.2	33.3 ± 10.5
Median	14.0	15.0	33.0	32.0
Range	9 – 16	11 – 16	17 – 76	17 - 65
Sex, n (%)				
Male	4 (21.1)	5 (20.0)	110 (51.2)	207 (47.3)
Female	15 (78.9)	20 (80.0)	105 (48.8)	231 (52.7)
White, n (%)	17 (89.5)	18 (72.0)	179 (83.3)	356 (81.3)
Baseline Disease Characteristics				
Sweat production (mg/5 min),[a] mean ± SD	151.7 ± 150.6	145.8 ± 133.4	178.4 ± 163.0	174.0 ± 219.5
ASDD/ASDD-C Item 2 (sweating severity), mean ± SD	6.7 ± 1.7	7.5 ± 1.2	7.2 ± 1.6	7.3 ± 1.6
HDSS, n (%)				
Grade 3	14 (73.7)	15 (60.0)	141 (65.6)	262 (59.8)
Grade 4	5 (26.3)	10 (40.0)	73 (34.0)	176 (40.2)
DLQI, mean ± SD	NA[c]	NA[c]	10.6 ± 5.9	11.9 ± 6.1
CDLQI,[b] mean ± SD	8.5 ± 5.6	9.9 ± 5.5	NA[c]	NA[c]

[a]Gravimetrically-measured average from the left and right axillae
[b]N=24 for GT group ≥9 to ≤16 years of age
[c]Patients ≥9 to ≤16 years of age were administered the CDLQI and patients >16 years of age were administered the DLQI
Intent-to-treat (ITT) population
ASDD, Axillary Sweating Daily Diary; ASDD-C, ASDD-Children; CDLQI, children's DLQI; DLQI, Dermatology Life Quality Index; GT, topical glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; NA, not applicable; SD, standard deviation

Short-Term Efficacy (Week 4)

- Efficacy results (ASDD Item 2 responder rate, gravimetric sweat production, HDSS responder rate, and DLQI/CDLQI) at Week 4 were consistent among the pediatric and older subgroups, with similar improvements in sweating severity, sweat production, and quality of life observed at Week 4, regardless of age
  - ASDD/ASDD-C Item 2 responder rates (≥4-point improvement from Baseline) were similar among GT-treated patients in the pediatric and older subgroups (59.9% versus 60.2%, respectively), and substantially greater for GT- versus vehicle-treated patients regardless of age subgroup (**Figure 3**)

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



Pooled ATMOS-1/ATMOS-2 data; intent-to-treat (ITT) population; P-values were not calculated for this post hoc analysis; multiple imputation (MCMC) was used to impute missing values; ASDD/ASDD-C was not assessed in ARIDO; therefore, there are no data available for comparison of short- versus long-term efficacy
ASDD, Axillary Sweating Daily Diary; ASDD-C, ASDD-Children; GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo

- Although GT-treated patients in the older subgroup had greater median absolute reduction from Baseline in gravimetrically-measured sweat production compared with the pediatric subgroup (-80.6 vs -64.2, respectively), GT-treated patients in both subgroups had greater median absolute change compared with vehicle-treated patients (**Table 2**)
- HDSS responder rate at Week 4 was similar among GT-treated pediatric and older subgroup patients (61.3% vs 58.7% of patients); both GT treatment groups had a markedly higher HDSS responder rate compared with the vehicle treatment groups (**Table 2**)
- Mean improvement from Baseline at Week 4 in CDLQI was consistent with that observed for DLQI in GT-treated patients in the pediatric and older subgroups (-8.1 vs -8.4); the vehicle response was greater in the older subgroup
  - Mean improvements in CDLQI and DLQI scores were approximately 4-fold and 2-fold greater, respectively, for GT-treated patients compared with vehicle-treated patients in each subgroup, indicating a positive impact of GT treatment on health-related quality of life (**Table 2**)

Table 2. Gravimetric Sweat Production, HDSS Responder Rate, and DLQI (Week 4)

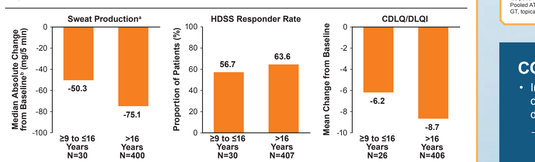
	≥9 to ≤16 Years		>16 Years	
	Vehicle N=19	GT N=25	Vehicle N=215	GT N=438
Median absolute change from Baseline in sweat production,[a] mg/5 min, mean ± SD	-53.7 ± 110.6	-64.2 ± 142.6	-62.0 ± 141.9	-80.6 ± 210.5
Proportion of patients achieving HDSS response (≥2-grade improvement from Baseline), %	20.3	61.3	26.0	58.7
Mean change from Baseline in CDLQI/DLQI				
CDLQI[b] (patients ≥9 to ≤16 years)	-1.9	-8.1	-----	-----
DLQI[c] (patients >16 years)	-----	-----	-4.7	-8.4

[a]Gravimetrically-measured average from the left and right axillae; [b]N=23 for GT; [c]n=206 and n=405 for vehicle and GT, respectively
Pooled ATMOS-1/ATMOS-2 data; intent-to-treat (ITT) population
P-values were not calculated for this post hoc analysis; multiple imputation (MCMC) was used to impute missing values for sweat production and HDSS responder rate
CDLQI, children's DLQI; DLQI, Dermatology Life Quality Index; GT, topical glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; MCMC, Markov chain Monte Carlo; SD, standard deviation

Long-Term Efficacy (Through Week 44)

- Through Week 44/ET in ARIDO (up to 48 weeks of GT from the start of the double-blind ATMOS-1/ATMOS-2 trials), improvements in efficacy measures, including sweat production, HDSS responder rate, and DLQI/CDLQI, were maintained, with similar results between the pediatric and older subgroups (**Figure 4**)
  - From Baseline in ATMOS-1/ATMOS-2 to Week 44/ET in ARIDO:
    - Median sweat production decreased by -50.3 and -75.1 mg/5 minutes in the pediatric and older subgroups, respectively, reflecting a maintenance of sweat reduction benefit (median decreases were 61.3 and 58.7 mg/5 minutes in GT-treated patients after 4 weeks of GT treatment in the double-blind trials)
    - The proportion of HDSS responders was consistent over the study course and similar to that observed after 4 weeks of GT treatment in the double-blind trials (59.9% and 60.2%, pediatric and older subgroups, respectively)
    - Mean DLQI and CDLQI scores improved by 8.7 ± 6.2 and 6.2 ± 4.9, which were maintained from a mean decrease of 8.4 ± 6.0 and 8.1 ± 5.4, respectively, in GT-treated patients after 4 weeks of treatment in ATMOS 1/ATMOS-2

Figure 4. ARIDO Outcomes at Week 44/End of Treatment



*Gravimetrically-measured average from the left and right axillae; †Baseline in ATMOS-1/ATMOS-2 for vehicle-treated and GT-treated patients who continued into ARIDO and received GT-treatment thereafter.
Pooled ATMOS-1/ATMOS-2 data; intent-to-treat (ITT) population
P-values were not calculated for this post hoc analysis; multiple imputation (MCMC) was used to impute missing values for sweat production and HDSS responder rate
CDLQI, children's DLQI; DLQI, Dermatology Life Quality Index; ET, end of treatment/early termination; GT, topical glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; MCMC, Markov chain Monte Carlo; SD, standard deviation

Safety

- Overall, GT was well tolerated across short and long-term treatment, and most adverse events were mild to moderate in severity, and infrequently led to discontinuation, regardless of age (**Table 3**)
  - Of two serious TEAEs reported in the double-blind trials, both occurred in the GT arm of the older subgroup and only one lead to discontinuation (moderate unilateral mydriasis; related to treatment)

Table 3. Safety Overview (Double-Blind Trials and Open-Label Extension By Age)

	Double-Blind Trials				Open-Label Extension	
	≥9 to ≤16 Years		>16 Years		≥9 to ≤16 Years	>16 Years
n* (%)	Vehicle N=19	GT N=25	Vehicle N=213	GT N=434	GT N=22	GT N=512
Any TEAE	2 (10.5)	11 (44.0)	73 (34.3)	246 (56.7)	22 (57.9)	307 (60.0)
Any Serious TEAE	0	0	0	2 (0.5)	0	7 (1.4)
Deaths	0	0	0	0	0	0
Discontinuation due to TEAE	0	1 (4.0)	1 (0.5)	17 (3.9)	1 (2.6)	42 (8.2)
TEAE by intensity						
Mild	2 (10.5)	6 (24.0)	51 (23.9)	164 (37.8)	14 (36.8)	134 (26.2)
Moderate	0	4 (16.0)	22 (10.3)	79 (18.2)	7 (18.4)	146 (28.5)
Severe	0	1 (4.0)	0	3 (0.7)	1 (2.6)	27 (5.3)

*Numbers in table represent the number of patients reporting ≥1 TEAE; not number of events
Pooled ATMOS-1/ATMOS-2 and ARIDO safety population
GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

- During both short and long-term treatment with GT, the majority of TEAEs reported in the GT group were related to anticholinergic activity
  - Anticholinergic TEAEs were similar between subgroups and between ATMOS-1/ATMOS-2 and ARIDO (**Table 4**)
    - The most frequently reported anticholinergic TEAE in GT-treated patients during both the double-blind trials and the open-label extension was dry mouth
    - Unlike mydriasis events in the older subgroup, which were largely unilateral (22 of 27 events), the majority of events in the pediatric subgroup were bilateral (3 of 4 events). Although difficult to determine given the small number of events, this may be attributed to pediatric patients being more likely to touch both eyes after GT application or possibly anticholinergic effects resulting from systemic exposure, which are minimized but not eliminated completely by topical GT application

Table 4. Anticholinergic-related TEAEs During the Double-Blind Trials and Open-Label Extension

	Double-Blind Trials				Open-Label Extension	
	≥9 to ≤16 Years		>16 Years		≥9 to ≤16 Years	>16 Years
n* (%)	Vehicle N=19	GT N=25	Vehicle N=213	GT N=434	GT N=38	GT N=512
Mydriasis	0	4 (16.0)[a]	0	27 (6.2)[d]	3 (7.9)[e]	26 (5.1)[f]
Vision blurred	0	3 (12.0)	0	13 (3.0)	4 (10.5)	33 (6.4)
Dry eye	0	1 (4.0)	1 (0.5)	10 (2.3)	0	16 (3.1)
Dry mouth	0	6 (24.0)	13 (6.1)	105 (24.2)	6 (15.8)	87 (17.0)
Urinary hesitation	0	0	0	16 (3.7)	1 (2.6)	22 (4.3)
Urinary retention	0	1 (4.0)	0	6 (1.4)	0	0
Nasal dryness	0	1 (4.0)	1 (0.5)	11 (2.5)	1 (2.6)	19 (3.7)
Constipation	0	0	0	9 (2.1)	1 (2.6)	7 (1.4)

*In either treatment arm in either age subgroup in the pooled population
†Numbers in table represent the number of patients reporting ≥1 TEAE; not number of events
[a]4 patients reported 1 unilateral event and 3 bilateral events
[d]27 patients reported 23 unilateral events and 5 bilateral events
[e]3 patients reported 3 unilateral events
[f]26 patients reported 26 unilateral events and 6 bilateral events
Pooled ATMOS-1/ATMOS-2 data; safety population
GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

CONCLUSIONS

- In this post hoc analysis of two large, 4-week, Phase 3 trials and their 44-week open-label extension, pediatric patients (≥9 to <16 years) treated once daily with GT demonstrated
  - Improved disease severity, reduced sweat production, and improved quality of life relative to vehicle at Week 4, with improvements maintained for an additional 44 weeks of open label GT
  - Similar efficacy findings to older patients
  - TEAE profile similar to older patients with TEAEs that were typically mild, and infrequently led to discontinuation
- The availability of topical, once-daily GT provides a noninvasive, effective treatment option for both adults and pediatric patients with primary axillary hyperhidrosis

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DISCLOSURES

AAH: Consultant for Dermira, Inc.; employee of the University of Texas Medical School, Houston, which received compensation from Dermira, Inc. for study participation. **DAG:** Consultant and investigator for Dermira, Inc. **LG:** Consultant and investigator for Dermira, Inc.; investigator for Brickell Biotech, Inc. **WPW:** Consultant and investigator for Dermira, Inc. **DP:** Consultant for Dermira, Inc.; Investigator for Jordan Valley Dermatology and Research Center. **JD, RG:** Employee of Dermira, Inc. **DMP:** Consultant and investigator for Dermira, Inc.

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