Onset of Action With Glycopyrronium Cloth in the Treatment of Primary Axillary Hyperhidrosis

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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]
- 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)[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]
- One of the outcomes in the Phase 3 trials utilized a daily patient diary, allowing for a detailed by-day assessment of patient reported sweating severity, impact, and bothersomeness in the first week of treatment

OBJECTIVE

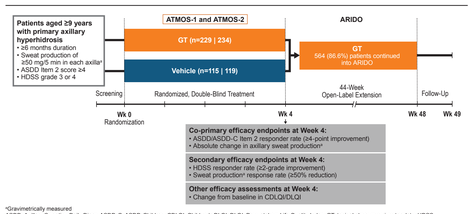
- To examine the timing of efficacy onset in the Phase 3 double-blind trials, pooled results were evaluated daily for the first seven days of treatment and using weekly averages thereafter through Week 4 (End of Study)

METHODS

ATMOS-1 and ATMOS-2 Study Design

- ATMOS-1 (sites in the US and Germany) and ATMOS-2 (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) patient-reported sweating severity (Item 2) score ≥4 (numeric scale 0-10), and Hyperhidrosis Disease Severity Scale (HDSS) ≥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. ATMOS-1/ATMOS-2 Study Design



*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

Efficacy and Safety Assessments

- Coprimary endpoints were
  - Responder rate (≥4-point improvement from Baseline) on Item 2 (sweating severity) of the ASDD
  - Absolute change from Baseline (cfB) in axillary sweat production (gravimetrically measured) at Week 4
- The ASDD is a newly developed 4-item patient-reported outcome (PRO)
  - A child-specific version of the ASDD (ASDD-C) consisting of the first 2 items 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]
    - A ≥4-point reduction in ASDD/ASDD-C Item 2 correlates with a Patient Global Impression of Change rating of at least 'moderately better', consistent with clinically meaningful change
  - In addition to Item 2 (sweating severity), ASDD items assess impact (Item 3) and bothersomeness (Item 4) of sweating
    - Items 3 and 4 are only administered to patients 16 years of age or older and are scored on a numeric scale from 0-4
    - No response threshold is defined for Items 3 and 4, so mean cfB was evaluated
  - All ASDD Item data were unique in that they were collected daily using an electronic diary throughout the trial, allowing for a detailed analysis of onset of effect within the first week of treatment
- Secondary efficacy endpoints included
  - HDSS responder rate (≥2-grade improvement from Baseline)
  - Gravimetrically-measured sweat production responder rate (≥50% reduction from Baseline; "Grav-50")
  - Absolute cfB gravimetric sweat production
- Safety was assessed via treatment-emergent adverse events (TEAEs)

Analyses

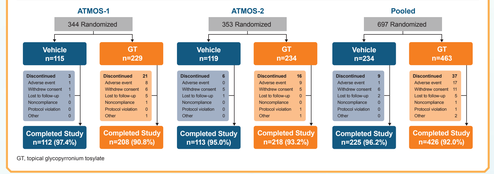
- Pooled ATMOS-1/ATMOS-2 ASDD/ASDD-C Item 2 scores were analyzed daily for the first seven days (post hoc) and weekly using averages for Weeks 2, 3, and 4 (prespecified)
  - Similar analyses were completed for ASDD Items 3 and 4
  - ASDD Items (2, 3, and 4) required at least 4 days of data per week to calculate weekly averages
- 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)
- The Markov chain Monte Carlo (MCMC) method for multiple imputation was used for missing efficacy data in the calculation of weekly scores; no data imputation was performed for the analysis of daily data
- Statistical comparison between GT and VEH on the two coprimary endpoints was prespecified for Week 4
  - ASDD/ASDD-C Item 2 responder rate was analyzed using the Cochran-Mantel-Haenszel (CMH) test
  - Absolute cfB in sweat production was analyzed using an analysis of covariance (ANCOVA) model applied to the cfB data subsequent to ranking with factors for treatment group and analysis center, and Baseline sweat production as a covariate
  - For secondary endpoints, a gated sequential procedure was used, first testing HDSS responder rate then testing sweat production responder rate using CMH tests stratified by analysis center
  - Post hoc analyses of ASDD/ASDD-C Item 2 response for days 1 to 7 were analyzed descriptively

RESULTS

Disposition, Demographics, and Baseline Disease Characteristics

- In the pooled population of the double-blind trials, 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 (median)	170.3 ± 164.2 (112.6)	182.9 ± 266.9 (122.1)	181.8 ± 160.1 (116.7)	162.3 ± 149.5 (126.8)	176.2 ± 161.9 (114.8)	172.5 ± 215.7 (124.6)
ASDD/ASDD-C 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
ASDD Item 3 (impact)	n=109	n=224	n=109	n=223	n=218	n=447
Mean ± SD	2.2 ±0.9	2.4 ±0.9	2.3 ±1.0	2.5 ±0.8	2.2 ±0.9	2.4 ±0.9
ASDD Item 4 (bothersomeness)	n=109	n=224	n=109	n=223	n=218	n=447
Mean ± SD	2.4 ±0.9	2.6 ±0.8	2.5 ±0.9	2.7 ±0.7	2.5 ±0.9	2.7 ±0.8
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	n=108 10.1 ± 5.9	n=220 12.1 ± 6.5	n=107 11.2 ± 5.8	n=218 11.6 ± 5.7	n=215 10.6 ± 5.9	n=438 11.9 ± 6.1
CDLQI (for patients ≤16 years of age),mean ± SD	n=7 6.9 ± 3.3	n=8 8.5 ± 6.5	n=12 9.5 ± 6.5	n=16 10.6 ± 5.1	n=19 8.5 ± 5.6	n=24 9.9 ± 5.5

ASDD, Axillary Sweating Daily Diary; 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

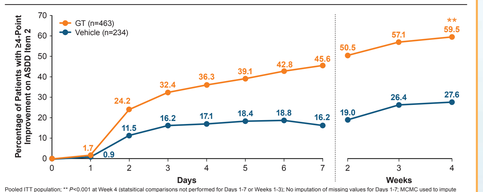
Efficacy: Co-Primary Endpoints

- A significant advantage for GT over VEH was observed on both co-primary endpoints ($P<0.001$; ASDD/ASDD-C Item 2 responder rate (≥4-point improvement from Baseline) and absolute change in sweat production at Week 4 in the pooled population)[3]

Efficacy: Daily and Weekly Findings (ASDD/ASDD-C Item 2)

- For the analyses evaluating daily ASDD/ASDD-C Item 2 responder rate over the first 7 days:
  - A markedly greater proportion of GT patients achieved ≥4-point ASDD/ASDD-C Item 2 improvement from Baseline starting on Day 2 vs VEH patients: Day 1 (1.7% vs 0.9%) and Day 2 (24.2% vs 11.5%) (**Figure 3**)
  - An increasingly higher proportion of GT-treated patients achieved ASDD/ASDD-C Item 2 response versus VEH throughout the remaining days of Week 1 (**Figure 3**)
- After Day 7, the proportion of ASDD/ASDD-C Item 2 responders continued to increase with GT versus VEH through the end of the trial, and was statistically significant at Week 4 (59.5% vs 27.6%; $P<0.001$; co-primary endpoint) (**Figure 3**)

Figure 3. Daily (Days 0-7) and Weekly ASDD/ASDD-C Item 2 Responder Rate (≥4-point improvement in sweating severity)

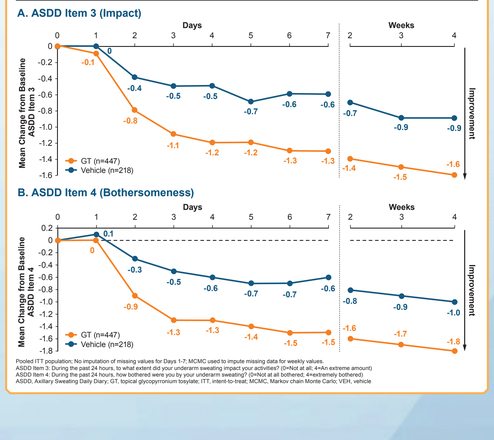


Pooled ITT population; ** $P<0.001$ at Week 4 (statistical comparisons not performed for Days 1-7 or Weeks 1-3); No imputation of missing values for Days 1-7; MCMC used to impute missing data for weekly values
ASDD, Axillary Sweating Daily Diary; GT, topical glycopyrronium tosylate; ITT, intent to treat; MCMC, Markov chain Monte Carlo; VEH, vehicle

Efficacy: Daily and Weekly Findings (ASDD Items 3 and 4)

- Mean change from baseline on ASDD Items 3 (impact) and 4 (bothersomeness) showed separation in favor of GT relative to VEH in the first seven days and through Week 4 (**Figure 4A and B**)

Figure 4. Daily (Days 0-7) and Weekly Change From Baseline in ASDD Item 3 (Impact) and Item 4 (Bothersomeness)

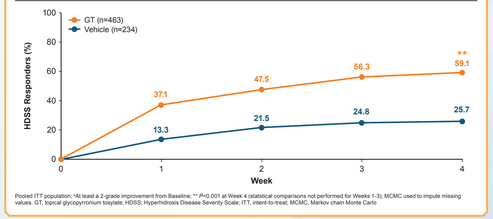


Pooled ITT population; No imputation of missing values for Days 1-7; MCMC used to impute missing data for weekly values.
ASDD Item 3: During the past 24 hours, to what extent did your underarm sweating impact your activities? (0=Not at all, 4=An extreme amount)
ASDD Item 4: During the past 24 hours, 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; ITT, intent-to-treat; MCMC, Markov chain Monte Carlo; VEH, vehicle

Efficacy: Weekly Findings (HDSS Responder Rate, Grav-50 Responder Rate, and Median Change Gravimetric Sweat Production)

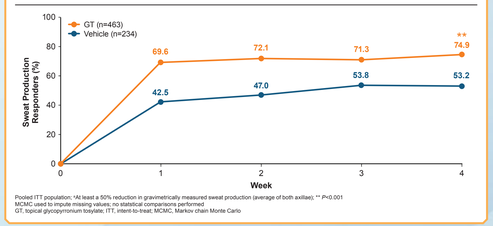
- The ASDD items were the only efficacy data collected daily during the trials; however, similar results were observed for additional efficacy assessments when evaluating patient outcomes by week
  - For HDSS and sweat production, the proportion of responders at Week 4 was significantly higher for GT versus vehicle ($P<0.001$ for each outcome in both trials),[3] a difference occurring as early as Week 1 (**Figures 5 and 6**; statistical comparisons not performed at Weeks 1-3)
  - Absolute reduction from baseline in sweat production was significantly greater with GT compared with VEH at Week 4 (co-primary endpoint; $P<0.001$ based on LS mean change), and separation was observed as early as Week 1 (statistical comparisons not performed for Weeks 1-3; **Figure 7**)

Figure 5. HDSS Responder Rate[a] Weeks 1-4



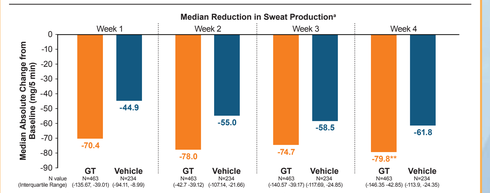
Pooled ITT population; [a]At least a 2-grade improvement from Baseline; ** $P<0.001$ at Week 4 (statistical comparisons not performed for Weeks 1-3); MCMC used to impute missing values. GT, topical glycopyrronium tosylate; HDSS: Hyperhidrosis Disease Severity Scale; ITT, intent-to-treat; MCMC, Markov chain Monte Carlo

Figure 6. Grav-50[a] Responder Rate Weeks 1-4



Pooled ITT population; [a]At least a 50% reduction in gravimetrically measured sweat production (average of both axillae); ** $P<0.001$
MCMC used to impute missing values; no statistical comparisons performed
GT, topical glycopyrronium tosylate; ITT, intent-to-treat; MCMC, Markov chain Monte Carlo

Figure 7. Absolute Reduction in Sweat Production from Baseline (Weeks 1-4)



N value (Interquartile Range) (-135.67, -39.01) (-94.11, -8.99) (-42.7, -39.12) (-107.14, -21.66) (-140.57, -39.17) (-117.69, -24.85) (-146.35, -42.85) (-113.5, -24.35)

Pooled ITT population; **P<0.001 at Week 4 (statistical comparisons not performed for Weeks 1-3) based on LS mean change from Baseline, *MCMC used to impute missing values
GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo

Safety

- Overall, GT was well tolerated, and most adverse events were mild to moderate in severity, and infrequently led to discontinuation (**Table 2; Figure 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)

	Pooled	
	Vehicle (N=232)	GT (N=459)
TEAEs, n (%)		
Any	75 (32.3)	257 (56.0)
Drug-related	38 (16.4)	179 (39.0)
Serious[a]	0	2 (0.4)
D/C due to TEAE, n (%)	1 (0.4)	17 (3.7)
Deaths, n (%)	0	0
TEAEs by intensity, n (%)		
Mild	53 (22.8)	170 (37.0)
Moderate	22 (9.5)	83 (18.1)
Severe	0	4 (0.9)
Anticholinergic TEAEs reported in >2% of patients,[b] n (%)		
Dry mouth	13 (5.6)	111 (24.2)
Mydriasis	0	31 (6.8)
Urinary hesitation	0	16 (3.5)
Dry eye	1 (0.4)	11 (2.4)
Vision blurred	0	16 (3.5)
Nasal dryness	1 (0.4)	12 (2.6)
Constipation	0	9 (2.0)
Urinary retention	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

- A notably higher proportion of patients reporting reductions in sweating severity (ASDD Item 2), and larger improvements from Baseline for impact (ASDD Item 3) and bothersomeness (ASDD Item 4) were observed in GT compared to VEH as early as Day 2 of treatment (post hoc analyses), consistent with an early onset of action
- Efficacy of GT (as assessed via responder rates for ASDD Item 2, HDSS, Grav-50, and absolute change from Baseline in sweat production; prespecified analyses) generally increased throughout the trial
  - The highest proportion of patients achieved response thresholds at Week 4 across multiple measures
- Daily GT treatment over 4 weeks was generally well tolerated in patients ≥9 years of age with primary axillary hyperhidrosis
- The availability of topical, once-daily GT provides a noninvasive, effective treatment option for primary axillary hyperhidrosis[2]

REFERENCES

1. Doolittle et al. *Arch Dermatol Res.* 2016;308(10):743-749. 2. QBREXZA™ (glycopyrronium) cloth [Prescribing Information]. Dermira, Inc., Menlo Park, CA. 2018. 3. Glaser et al. *Journal of the American Academy of Dermatology.* 2018 (In preparation). 4. Glaser et al. Poster presented at 13th Annual Maui Derm for Dermatologists; 2017; Maui, HI.

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DISCLOSURES

DMP: Consultant and Investigator for Dermira, Inc. **LG:** Investigator for Brickell; Advisory Board member and investigator for Dermira. **JD:** Employee of Dermira, Inc. **RG:** Employee of Dermira, Inc. **VY:** Employee of Dermira, Inc. **DAG:** Consultant and Investigator for Dermira,

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