Patient-Reported Outcomes From Two Randomized, Double-Blind, Vehicle-Controlled Phase 3 Trials in Axillary Hyperhidrosis (ATMOS-1 & ATMOS-2)

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INTRODUCTION

- Hyperhidrosis affects an estimated 4.8% of the US population, or approximately 15.3 million people, and negative psychological consequences are experienced by approximately 75% of patients with the disorder[1]
- The prevalence of anxiety and depression is over 3.5 times greater in people with hyperhidrosis than in those without it, and there is a positive correlation between the severity of hyperhidrosis and rates of anxiety and depression[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 clinical trials (ATMOS-1 [sites in the US and Germany] and ATMOS-2 [US sites only]); the primary efficacy and safety results of these studies have been previously reported[3]
- Patient-reported outcomes (PROs) from these pivotal trials were also assessed using the 4-item Axillary Sweating Daily Diary (ASDD),[4] 6 Weekly Impact Items, and the single-item Patient Global Impression of Change (PGIC) that were developed according to current regulatory standards
  - The ASDD/ASDD-C axillary sweating severity item (Item 2) was specifically developed for use as an endpoint in clinical trials in support of approval and labeling (also as a useful clinical parameter)

OBJECTIVE

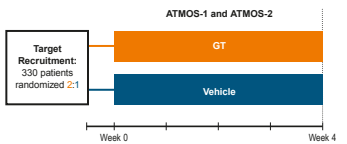
- To evaluate changes in patient-reported outcomes after 4 weeks of treatment with GT compared with vehicle in ATMOS-1 and ATMOS-2

METHODS

ATMOS-1 and ATMOS-2 Study Design

- ATMOS-1 (DRM04-HH04; NCT02530281) and ATMOS-2 (DRM04-HH05; NCT02530294) 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 (**Figure 1**)
  - Coprimary endpoints included ASDD axillary sweating severity item (Item 2) responder rate (defined as ≥4-point improvement from Baseline) at Week 4 and mean absolute change from Baseline in gravimetrically-measured sweat production at Week 4
- 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, ASDD Item 2 score ≥4, and Hyperhidrosis Disease Severity Scale (HDSS) grade 3 or 4
- 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 for axillary hyperhidrosis within 1 year; 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



Patient-Reported Outcomes

- Axillary Hyperhidrosis Patient Measures (AHPM)
  - The ASDD consists of 4 items and was used for patients ≥16 years; patients <16 years of age completed a modified, 2-item version of the ASDD, the ASDD-C (**Table 1**)
  - Patients ≥16 years were additionally asked to complete 6 Weekly Impact items and a single-item Patient Global Impression of Change (PGIC) (**Table 1**)
- Mean changes from Baseline were summarized by descriptive statistics in the intent-to-treat (ITT) population (all randomized subjects who were dispensed study drug)
  - For ASDD Item 2 (all patients) and ASDD items related to the impact and bother of axillary sweating (Items 3 and 4, respectively; patients ≥16 years of age), Baseline was defined as the average of ≥4 days of data in the most recent 7 days prior to randomization
  - For the Weekly Impact items (patients ≥16 years of age), Baseline was defined as the last available record prior to Day 1
  - As the PGIC was only administered at the end of study treatment, there was no Baseline value
- Missing values for ASDD Items 2 through 4 were not imputed; for Weekly Impact Items, the last observation carried forward (LOCF) approach was used to impute missing values
- An additional analysis was performed to assess the percent improvement from Baseline to Week 4 in ASDD Item 2, 3, and 4 scores

Table 1. Axillary Hyperhidrosis Patient Measures (AHPM)[a]

Axillary Sweating Daily Diary (ASDD)[b]	
Instructions: The questions in the diary are designed to measure the severity and impact of any underarm sweating you have experienced within the previous 24 hour period, including nighttime hours. While you may also experience sweating in other locations on your body, please be sure to think only about your underarm sweating when answering these questions. Please complete the diary each evening before you go to sleep.	
Item 1 [Gatekeeper]	**During the past 24 hours**, did you have **any** underarm sweating? Yes/No. When Item 1 is answered "no," Item 2 is skipped and scored as zero
Item 2	**During the past 24 hours**, how would you rate your underarm sweating at its worst? *0 (no sweating at all) to 10 (worst possible sweating)*
Item 3	**During the past 24 hours**, to what extent did your underarm sweating impact your activities? *0 (not at all), 1 (a little bit), 2 (a moderate amount), 3 (a great deal), 4 (an extreme amount)*
Item 4	**During the past 24 hours**, how bothered were you by your underarm sweating? *0 (not at all bothered), 1 (a little bothered), 2 (moderately bothered), 3 (very bothered), 4 (extremely bothered)*
Axillary Sweating Daily Diary-Children (ASDD-C)[c]	
Instructions: These questions measure how bad your underarm sweating was last night and today. Please think only about your underarm sweating when answering these questions. Please complete these questions each night before you go to sleep.	
Item 1 [Gatekeeper]	Thinking about **last night and today**, did you have any underarm sweating? Yes/No. When Item 1 is answered "no," Item 2 is skipped and scored as zero
Item 2	Thinking about **last night and today**, how bad was your underarm sweating? *0 (no sweating at all) to 10 (worst possible sweating)*
Weekly Impact Items[b]	
Instructions: Please respond "Yes" or "No" to each of the following questions.	
a. **During the past 7 days**, did you *ever* have to change your shirt during the day because of your underarm sweating?	Yes/No
b. **During the past 7 days**, did you *ever* have to take more than 1 shower or bath a day because of your underarm sweating?	Yes/No
c. **During the past 7 days**, did you *ever* feel less confident in yourself because of your underarm sweating?	Yes/No
d. **During the past 7 days**, did you *ever* feel embarrassed by your underarm sweating?	Yes/No
e. **During the past 7 days**, did you *ever avoid* interactions with other people because of your underarm sweating?	Yes/No
f. **During the past 7 days**, did your underarm sweating ever keep you from doing an activity you wanted or needed to do?	Yes/No
Patient Global Impression of Change (PGIC) Item[b]	
Overall, how would you rate your underarm sweating now as compared to before starting the study treatment? *1 (much better), 2 (moderately better), 3 (a little better), 4 (no difference), 5 (a little worse), 6 (moderately worse), 7 (much worse)*	

[a]ASDD/ASDD-C Item 2 is a validated PRO measure
[b]For use in patients ≥16 years of age
[c]For use in patients ≥9 to < 16 years of age

RESULTS

- A total of 697 patients were randomized and were asked ASDD/ASDD-C Items 1 and 2 on a daily basis; 665 patients were ≥16 years of age and were asked ASDD items related to the impact and burden of sweating on a daily basis (Items 3 and 4, respectively), the Weekly Impact Items on a weekly basis, and the PGIC at end of treatment
- Demographic and Baseline disease characteristics from the primary studies are presented in **Table 2**

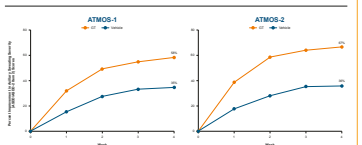
Table 2. Demographics and Baseline Disease Characteristics

	ATMOS-1		ATMOS-2	
	Vehicle (N=115)	GT (N=229)	Vehicle (N=119)	GT (N=234)
Demographics				
Age (years), mean ± SD	34.0 ± 13.1	32.1 ± 11.2	32.8 ± 11.2	32.6 ± 10.9
Age group, n (%) <16 years	6 (5.2)	5 (2.2)	10 (8.4)	11 (4.7)
≥16 years	109 (94.8)	224 (97.8)	109 (91.6)	223 (95.3)
Male, n (%)	55 (47.8)	99 (43.2)	59 (49.6)	113 (48.3)
White, n (%)	94 (81.7)	182 (79.5)	102 (85.7)	192 (82.1)
BMI (kg/m²), mean ± SD	27.2 ± 4.9	27.6 ± 5.8	28.4 ± 5.5	27.3 ± 5.0
Baseline Disease Characteristics, mean ± SD				
Years with primary axillary hyperhidrosis	16.0 ± 11.4	13.7 ± 10.4	15.9 ± 9.9	16.9 ± 11.1
Sweat production (mg/5 min)[a]	170.3 ± 164.2	182.9 ± 266.9	181.9 ± 160.1	162.3 ± 149.5
ASDD/ASDD-C Item 2 (Severity)	7.1 ± 1.7	7.3 ± 1.6	7.2 ± 1.6	7.3 ± 1.6
ASDD Item 3 (Impact)[b]	2.2 ± 0.9	2.4 ± 0.9	2.3 ± 1.0	2.5 ± 0.8
ASDD Item 4 (Burden)[b]	2.4 ± 0.9	2.6 ± 0.8	2.5 ± 0.9	2.7 ± 0.9

[a]Gravimetrically-measured
[b]Mean Baseline scores for ASDD Items 3 and 4 are based on all patients in the ITT populations of ATMOS-1 and ATMOS-2 ≥16 years of age only
Baseline scores for Items 2 to 4 were based on the average of ≥4 days of data in the most recent 7 days prior to randomization
ASDD, Axillary Sweating Daily Diary; ASDD-C, ASDD-Children; BMI, body mass index; GT, topical glycopyrronium tosylate

- The ASDD Item 2 responder rate (coprimary outcome; ≥4-point improvement) was significantly greater for GT-treated patients than for vehicle-treated patients in ATMOS-1 (53% vs 28%) and ATMOS-2 (66% vs 27%) (p<0.001 both studies)
- Improvement in axillary sweating severity (ASDD/ASDD-C Item 2) was greater for GT-treated patients compared with vehicle-treated patients at every study week (**Figure 2**)
  - After 4 weeks of treatment in ATMOS-1, scores improved 58% (-4.3 point change) in GT-treated patients and 35% (-2.5) in vehicle-treated patients compared with Baseline
  - After 4 weeks of treatment in ATMOS-2, scores improved 67% (-4.9 point change) in GT-treated patients and 36% (-2.6) in vehicle-treated patients compared with Baseline

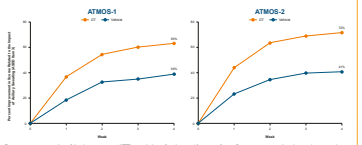
Figure 2. Percent Improvement From Baseline in Axillary Sweating Severity (ASDD/ASDD-C Item 2) Scores by Week



Data are representative of the intent-to-treat (ITT) population; figures represent the change in scores in terms of percent improvement
ASDD Item 2: **During the past 24 hours**, how would you rate your underarm sweating at its worst? *0 (no sweating at all) to 10 (worst possible sweating)*
ASDD-C Item 2: Thinking about **last night and today**, how bad was your underarm sweating? *0 (no sweating at all) to 10 (worst possible sweating)*
ASDD, Axillary Sweating Daily Diary; ASDD-C, ASDD-Children; GT, topical glycopyrronium tosylate

- Improvement in scores related to the impact of axillary sweating (ASDD Item 3) scores was greater for GT-treated patients than vehicle-treated patients at every study week (**Figure 3**)
  - After 4 weeks of treatment in ATMOS-1, scores improved by 63% (-1.5 point change) in GT-treated patients and 39% (-0.8) in vehicle-treated patients compared with Baseline
  - After 4 weeks of treatment in ATMOS-2, scores improved by 72% (-1.7 point change) in GT-treated patients and 41% (-1.0) in vehicle-treated patients compared with Baseline

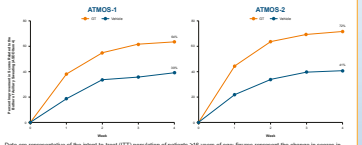
Figure 3. Percent Improvement From Baseline in Scores Related to the Impact of Axillary Sweating (ASDD Item 3) by Week



Data are representative of the intent-to-treat (ITT) population of patients ≥16 years of age; figures represent the change in scores in terms of percent improvement
ASDD Item 3: **During the past 24 hours**, to what extent did your underarm sweating impact your activities? *0 (not at all), 1 (a little bit), 2 (a moderate amount), 3 (a great deal), 4 (an extreme amount)*
ASDD, Axillary Sweating Daily Diary; GT, topical glycopyrronium tosylate

- Improvement in scores related to the bother of axillary sweating (ASDD Item 4) was greater in GT-treated patients than vehicle-treated patients at every study week (**Figure 4**)
  - After 4 weeks of treatment in ATMOS-1, Item 4 scores improved by 64% (-1.7 point change) in GT-treated patients and by 39% (-0.9) in vehicle-treated patients compared with Baseline
  - After 4 weeks of treatment in ATMOS-2, Item 4 scores improved by 72% (-1.9 point change) in GT-treated patients and by 41% (-1.0) in vehicle-treated patients compared with Baseline

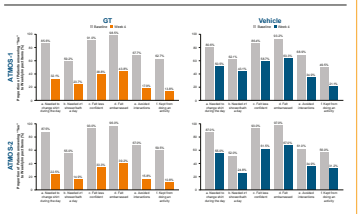
Figure 4. Percent Improvement From Baseline in Scores Related to the Bother of Axillary Sweating (ASDD Item 4) by Week



Data are representative of the intent-to-treat (ITT) population of patients ≥16 years of age; figures represent the change in scores in terms of percent improvement
ASDD Item 4: **During the past 24 hours**, how bothered were you by your underarm sweating? *0 (not at all bothered), 1 (a little bothered), 2 (moderately bothered), 3 (very bothered), 4 (extremely bothered)*
ASDD, Axillary Sweating Daily Diary; GT, topical glycopyrronium tosylate

- The proportion of patients who were negatively impacted by aspects of sweating (Weekly Impact items) decreased at Week 4 for all patients regardless of treatment; the magnitude of the decrease was greater in patients treated with GT than with vehicle on all items, indicating greater improvement with GT treatment (**Figure 5**)

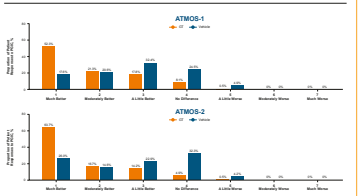
Figure 5. Proportion of Patients Answering 'Yes' to Weekly Impact Items



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

- Following treatment in ATMOS-1 and ATMOS-2, 73.6% and 80.4% of GT-treated patients rated their axillary sweating as much or moderately better, compared with 38.2% and 40.6% of vehicle-treated patients, respectively (**Figure 6**)
- Following treatment in ATMOS-1 and ATMOS-2, more vehicle-treated patients (29.4% and 36.5%, respectively) reported no difference or a little worsening in axillary sweating following treatment compared with those receiving GT (8.6% and 5.4%, respectively)

Figure 6. Distribution of Patient Responses to PGIC



Data are representative of the intent-to-treat (ITT) population of patients ≥16 years of age
PCIG Item: Overall, how would you rate your underarm sweating now as compared to before starting the study treatment? *1 (much better), 2 (moderately better), 3 (a little better), 4 (no difference), 5 (a little worse), 6 (moderately worse), 7 (much worse)*
GT, topical glycopyrronium tosylate; PCIG, Patient Global Impression of Change

CONCLUSIONS

- After 4 weeks, GT-treated patients reported greater weekly average improvement than vehicle-treated patients on all ASDD items (ie, severity, impact, and bother of axillary sweating on daily activities) that measured the daily burden of disease associated with axillary hyperhidrosis
- At the end of treatment, fewer GT-treated patients reported the occurrence of the specific negative behaviors or feelings associated with their excessive axillary sweating than did vehicle-treated patients
- Following treatment, approximately 2-fold more GT-treated patients rated their axillary sweating as much or moderately better versus vehicle-treated patients
- These additional results from ATMOS-1 and ATMOS-2 suggest that GT, if approved, has the potential to reduce the burden of disease for patients with axillary hyperhidrosis

References

1. Doolittle et al. *Arch Dermatol Res.* 2016; 308 (10):743-9. **2.** Bahar et al. *J Am Acad Dermatol.* 2016; 75(6):1126-33. **3.** Pariser et al. Poster presented at: 25th European Academy of Dermatology and Venereology Congress; September 28-October 2, 2016; Vienna, Austria. **4.** Pariser et al. Poster presented at: 13th Annual Maui Derm for Dermatologists; March 20-24, 2017; Maui, HI.

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