Topical glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: Results from the ATMOS-1 and ATMOS-2 phase 3 randomized controlled trials

Dee Anna Glaser, MD,[a] Adelaide A. Hebert, MD,[b] Alexander Nast, MD,[c] William P. Werschler, MD,[d] Lawrence Green, MD,[e] Richard Mamelok, MD,[f] Janice Drew, MPH,[g] John Quiring, PhD,[h] and David M. Pariser, MD[i]

St. Louis, Missouri; Houston, Texas; Berlin, Germany; Spokane, Washington; Washington, DC; Palo Alto and Menlo Park, California; Allendale, Michigan; and Norfolk, Virginia

Background: Glycopyrronium tosylate (GT) is a topical anticholinergic developed for once-daily treatment of primary axillary hyperhidrosis.

Objective: Assess the efficacy and safety of GT for primary axillary hyperhidrosis.

Methods: ATMOS-1 and ATMOS-2 were replicate randomized, double-blind, vehicle-controlled, 4-week phase 3 trials. Patients were randomized 2:1 to GT 3.75% or vehicle applied once daily to each axilla for 4 weeks. Coprimary endpoints were responder rate (≥4-point improvement from baseline) on item 2

From Saint Louis University, St. Louis[a]; UTHealth McGovern Medical School, Houston[b]; Charité—Universitätsmedizin Berlin[c]; Premier Clinical Research, Spokane[d]; George Washington University School of Medicine, Washington, DC[e]; Mamelok Consulting, Palo Alto[f]; Dermira, Inc, Menlo Park[g]; QST Consultations, Allendale[h]; and Eastern Virginia Medical School and Virginia Clinical Research, Inc, Norfolk.[i]

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Reprint requests: Dee Anna Glaser, MD, Saint Louis University, 1755 S Grand Blvd, St. Louis, MO 63104. E-mail: glasermd@slu.edu.

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(severity of sweating) of the Axillary Sweating Daily Diary (ASDD), which is a newly developed patient-reported outcome measure, and absolute change from baseline in axillary gravimetric sweat production at week 4. Safety evaluation included treatment-emergent adverse events.

Results: Pooled data, which are consistent with the individual trial results, show that significantly more GT-treated patients achieved an ASDD-Item 2 response than did those treated with vehicle (59.5% vs 27.6%), and they had reduced sweat production from baseline (−107.6 mg/5 min vs −92.1 mg/5 min) at week 4 ($P < .001$ for both coprimary end points). Most treatment-emergent adverse events were mild or moderate and infrequently led to discontinuation.

Limitations: Short trial duration and inherent challenges in gravimetrically assessing sweat production.

Conclusions: GT applied topically on a daily basis over 4 weeks reduced the severity of sweating as measured by ASDD-Item 2, reduced sweat production as measured gravimetrically, and was generally well tolerated in patients with primary axillary hyperhidrosis. (J Am Acad Dermatol 2019;80:128-38.)

Key words: anticholinergic; axilla; cholinergic receptor; DRM04; glycopyrronium tosylate; hyperhidrosis; sweat.

CAPSULE SUMMARY

- Current treatment options for hyperhidrosis are limited.
- The topical anticholinergic glycopyrronium tosylate resulted in significant reductions in severity of sweating and sweat production with favorable tolerability in 2 phase 3 randomized, vehicle-controlled trials in patients with primary axillary hyperhidrosis.
- Glycopyrronium tosylate, now approved by the US FDA, is a noninvasive, once-daily, topical treatment option for primary axillary hyperhidrosis.

Hyperhidrosis, which is a condition characterized by sweat production exceeding that which is necessary to maintain normal thermal homeostasis, has an estimated prevalence in the United States of 4.8% (~15.3 million people).[1,2] The adverse impact of hyperhidrosis on quality of life has been well documented,[2-6] and a recent case-control study found that anxiety and depression are more than 3.5 times more prevalent among patients with hyperhidrosis than among those without it.[7]

Hyperhidrosis treatments have included nonsurgical and surgical options that generally work to block sweat from reaching the skin surface (eg, antiperspirants), inhibit neuronal transduction to sweat glands (eg, onabotulinum toxinA or oral anticholinergic drugs), or destroy the sweat glands (eg, thermal ablation or surgical removal) or work via unknown mechanisms (eg, iontophoresis).[2,8,9] These treatments vary greatly with respect to effectiveness, invasiveness, and side effects and prior to 2018 only 2 had been approved by the US Food and Drug Administration (FDA) for axillary hyperhidrosis (onabotulinum toxin A and a microwave device for thermal ablation of sweat glands). Although treatment regimens may vary according to patient characteristics and symptom severity,[2] patients generally remain unsatisfied with the currently available treatment options.[5,10,11] Patients with hyperhidrosis often delay or avoid seeking treatment, likely owing to a lack of recognition of hyperhidrosis as a medical condition, the social stigma of excessive sweating, and/or low levels of satisfaction with or awareness of available treatments.[5,10,11]

Glycopyrronium tosylate (GT [formerly DRM04]) is a topical anticholinergic approved by the US Food and Drug Administration (June 29, 2018) for primary axillary hyperhidrosis in patients 9 years and older (glycopyrronium cloth, 2.4%, for topical use). GT is applied once daily to the axillae by using a premoistened towelette. ATMOS-1 and ATMOS-2 (registered as NCT02530281 and NCT02530294, respectively, at ClinicalTrials.gov on August 21, 2015) were replicate, phase 3 trials designed to assess efficacy and safety of GT when applied once daily for 4 weeks in patients who were at least 9 years of age and had primary axillary hyperhidrosis. These trials are, to our knowledge, the first phase 3 use of the Axillary Sweating Daily Diary (ASDD), which assess severity, impact, and bothersomeness of axillary hyperhidrosis.[12] The ASDD was developed in consultation with the FDA and the 2009 FDA guidance on patient-reported

Abbreviations used:

AHPM:	Axillary Hyperhidrosis Patient Measures
ASDD:	Axillary Sweating Daily Diary
ASDD-C:	Axillary Sweating Daily Diary-Children
CfB:	change from baseline
FDA:	US Food and Drug Administration
GT:	glycopyrronium tosylate
HDSS:	Hyperhidrosis Disease Severity Scale
LSR:	local skin reaction
PRO:	patient-reported outcome
TEAE:	treatment-emergent adverse event

outcomes (PROs).[13] Evidence supporting validity of the ASDD has been reported,[12] along with a description of several other PRO measures, which are collectively referred to here as the Axillary Hyperhidrosis Patient Measures (AHPM) (Supplemental Fig 1; available at http://www.jaad.org). The assessments that are part of the AHPM, in combination with gravimetric measurement of sweat production, were utilized to provide a thorough assessment of GT efficacy.

MATERIALS AND METHODS

ATMOS-1 was conducted in the United States and Germany; ATMOS-2 was conducted in the US. Trial protocols, and informed consent forms, were approved by local institutional review boards or independent ethics committees on May 13, 2015. The first patients were enrolled in July 2015 (ATMOS-1) and August 2015 (ATMOS-2); both trials were carried out in accordance with Good Clinical Practice[14] and the Declaration of Helsinki.[15]

Study design

ATMOS-1 and ATMOS-2 were replicate, phase 3, randomized, double-blind, vehicle-controlled, parallel-group, 4-week trials (Fig 1). After a 35-day screening period and treatment washout, eligible patients were randomized (2:1) via a central interactive web-based system to GT 3.75% (equivalent to 2.4% glycopyrronium) or matching vehicle, with treatment allocation balanced primarily within study centers. The sponsor, clinical research organization, investigator, study center personnel, and subjects were blinded to treatment assignment, and the integrity of the blind was maintained throughout the study. Patients applied the investigational product once daily to clean, dry skin of both axillae for 4 weeks and were not allowed to wash the area for 4 hours after application; missed doses could be applied within a 12-hour window until the next scheduled application. Patients were assessed at the clinic at weeks 1, 2, 3, and 4 (end of treatment) and via telephone for safety follow-up at week 5 for those patients not continuing in an open-label extension trial (ARIDO). A nonmedicated deodorant supplied for use during study participation could be applied if it was removed before gravimetric measurement of sweat production. Subjects could shave or closely clip hair in each axilla on the morning of each dosing day.

Patients

The patients were male or nonpregnant females who were at least 9 years of age (≥18 years in Germany) with primary axillary hyperhidrosis for at least 6 months, sweat production (determined by gravimetric analysis as discussed later in this article) of at least 50 mg within 5 minutes in each axilla at least once during up to 3 measurements performed within the 35-day prerandomization period, ASDD severity of sweating (item 2) score of 4 or higher, and Hyperhidrosis Disease Severity Scale[16] (HDSS) grade 3 or 4 (on a 4-point scale).

Patients were excluded for history of a condition that could cause secondary hyperhidrosis or be exacerbated by the trial medication, a prior surgical procedure for hyperhidrosis, a prior axillary treatment with an antihyperhidrosis medical device within 4 weeks of baseline, treatment with botulinum toxin within 1 year of baseline, or other treatments with anticholinergic activity within 4 weeks of baseline unless the dosing was stable for at least 4 months before baseline.

Efficacy and safety assessments

The AHPM includes 3 assessments: the ASDD, 6 weekly impact items, and a single-item Patient Global Impression of Change (Supplemental Fig 1).[12] The ASDD is a 4-item PRO measure to be completed daily by patients age 16 years or older. A child-specific version of the ASDD, called the Axillary Sweating Daily Diary-Children (ASDD-C) and consisting of the first 2 items, was utilized for patients who were at least 9 but less than 16 years of age.[12] ASDD Item 2 is an 11-point numeric rating scale of severity of sweating. All AHPM assessments were completed by patients with use of an electronic tablet.

The coprimary efficacy end points were the proportion of patients achieving an ASDD/ASDD-C Item 2 response, defined as a 4-point or greater improvement in weekly average responses from baseline (corresponding to Patient Global Impression of Change rating of moderately better[12] at week 4 and mean absolute change from baseline (CfB) in sweat production (average of both axillae) at week 4. Gravimetric assessments were conducted in the clinic under controlled conditions, and all

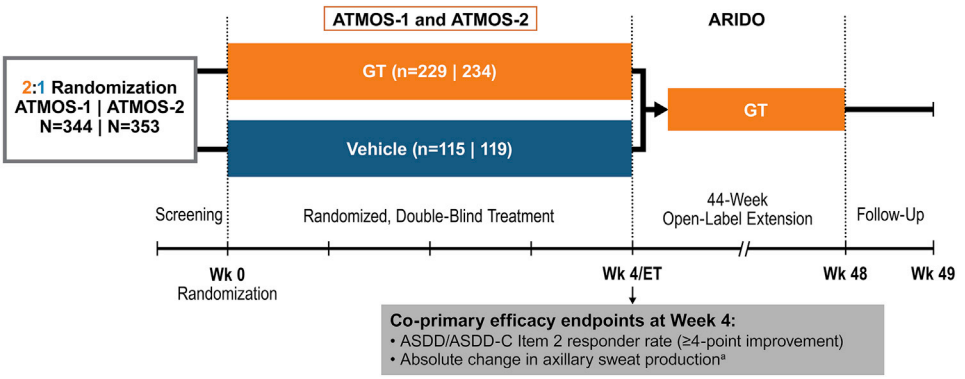

Fig 1. Hyperhidrosis: study design. For subjects not enrolling in ARIDO, telephone follow-up occurred in week 5 to record adverse events and concomitant medications. [a]Gravimetrically measured. *ASDD*, Axillary Sweating Daily Diary; *ASDD-C*, Axillary Sweating Daily Diary-Children; *ET*, end of treatment for ATMOS-1 and ATMOS-2; *GT*, glycopyrronium tosylate.

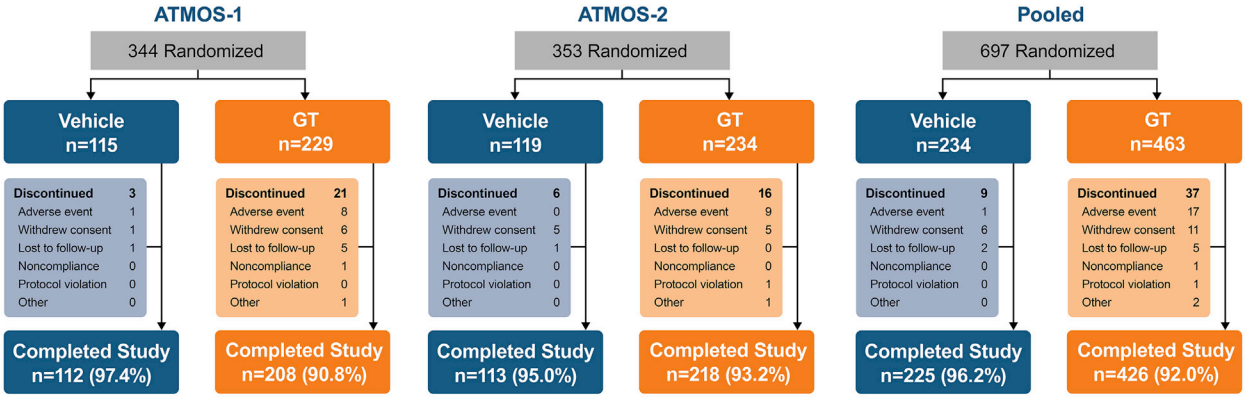

Fig 2. Hyperhidrosis: study design and patient disposition. *GT*, Glycopyrronium tosylate.

equipment was standardized across study sites. The room used for the gravimetric procedure was temperature-regulated (70°F-76°F [21°C-24°C]), and the humidity was kept constant at each site; sweat was collected after the patient had acclimated to the controlled environment for approximately 30 minutes. The secondary efficacy end points were HDSS responder rate (≥2-grade improvement from baseline) and sweat production responder rate (≥50% reduction from baseline) at week 4. A 2-point improvement in HDSS score has been associated with an 80% reduction in sweat production.[16] Other end points included the Dermatology Life Quality Index (patients >16 years of age) and the Children's Dermatology Life Quality Index (patients 9-16 years of age).

Safety was assessed through treatment-emergent adverse events (TEAEs) and local skin reactions (LSRs), laboratory testing results, vital signs, electrocardiogram results, and physical examination findings. TEAEs of special interest were defined (on the basis of association with systemic anticholinergic compounds) as blurry vision, mydriasis, and symptoms associated with urinary hesitancy and/or retention.

Statistical analysis

Sample size was based on gravimetric estimates of sweat production from 2 phase 2 studies of GT. With use of a 2:1 (GT-to-vehicle) randomization ratio, an overall sample size of 330 in each trial was required to provide 95% power at a significance level of .05 for the sweat production coprimary end point. If fewer than 12 patients were enrolled at an investigational site, data from that site were combined with data from other sites to achieve the minimum sample size, thereby creating "analysis centers" that were used as a factor in the analyses.

Efficacy analyses were conducted with the intent-to-treat population (all patients who were randomized and given the trial drug). The ASDD/ASDD-C Item 2 responder rate was analyzed by using the Cochran-Mantel-Haenszel test stratified by analysis center. Absolute CfB in sweat production was analyzed by using an analysis of covariance

Table I. Patient demographics and baseline disease characteristics (ITT population)

Patient and 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, y, 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 y	6 (5.2)	5 (2.2)	10 (8.4)	11 (4.7)	16 (6.8)	16 (3.5)
≥16 y	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)
Black or African American, n (%)	16 (13.9)	31 (13.5)	14 (11.8)	28 (12.0)	30 (12.8)	59 (12.7)
Asian, n (%)	0 (0)	4 (1.7)	0 (0)	1 (0.4)	0 (0)	5 (1.1)
BMI (kg/m^2), mean ± SD	27.2 ± 4.9	27.6 ± 5.8	28.4 ± 5.5	27.3 ± 5.0	27.8 ± 5.2	27.5 ± 5.4
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	84 (73.0)	133 (58.1)	71 (59.7)	144 (61.5)	155 (66.2)	277 (59.8)
Grade 4	31 (27.0)	96 (41.9)	47 (39.5)	90 (38.5)	78 (33.3)	186 (40.2)
DLQI (for patients >16 y of age), mean ± SD	10.1 ± 5.9 (n = 108)	12.1 ± 6.5 (n = 220)	11.2 ± 5.8 (n = 107)	11.6 ± 5.7 (n = 218)	10.6 ± 5.9 (n = 215)	11.9 ± 6.1 (n = 438)
CDLQI (for patients ≤16 y of age), mean ± SD	6.9 ± 3.3 (n = 7)	8.5 ± 6.5 (n = 8)	9.5 ± 6.5 (n = 12)	10.6 ± 5.1 (n = 16)	8.5 ± 5.6 (n = 19)	9.9 ± 5.5 (n = 24)

ASDD, Axillary Sweating Daily Diary; *BMI*, body mass index; *CDLQI*, Children's Dermatology Life Quality Index; *DLQI*, Dermatology Life Quality Index; *GT*, glycopyrronium tosylate; *HDSS*, Hyperhidrosis Disease Severity Scale; *ITT*, intent-to-treat; *SD*, standard deviation.
*Gravimetrically measured average of the right and left axillae.

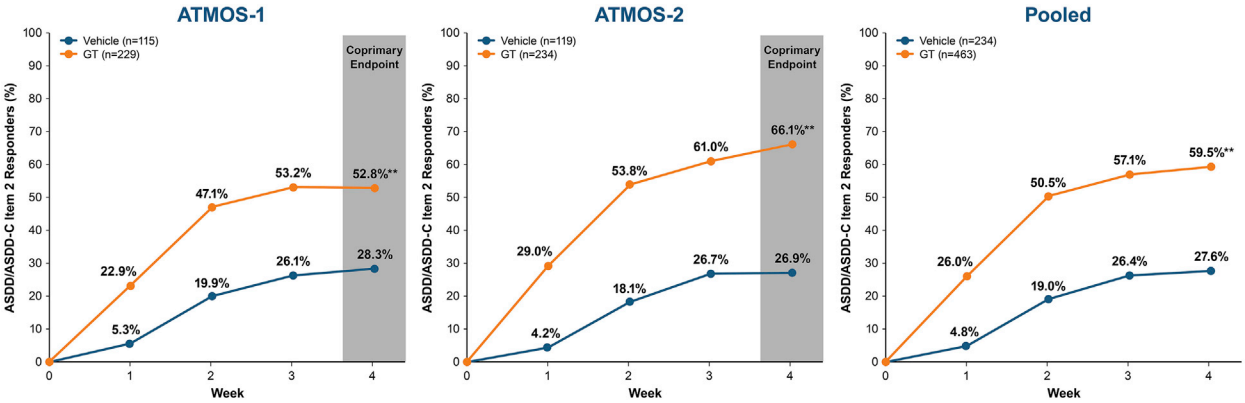

Fig 3. Hyperhidrosis: proportion of patients with at least a 4-point improvement from baseline on the Axillary Sweating Daily Diary/Axillary Sweating Daily Diary-Children Item 2 (sweating severity). Data are for the intent-to-treat population. The Markov chain Monte Carlo method was used for multiple imputation of missing data; *P* value was calculated for glycopyrronium tosylate (GT) versus vehicle by using of the Cochran-Mantel-Haenszel test with stratification by analysis center at week 4 (*P* values were calculated only for week 4; the *P* values for the pooled analysis are nominal). $^{**}P < .001$.

model applied to the CfB data subsequent to ranking with factors for treatment group and analysis center and with baseline sweat production as a covariate. For secondary end points, a gated sequential procedure was used, first testing the HDSS responder rate and then testing the sweat production responder rate via use of Cochran-Mantel-Haenszel tests stratified by analysis center for each. A sensitivity analysis was prespecified for primary end points to allow for identification of analysis centers with outlier data and exclusion of those centers from the primary analysis. Safety analyses were conducted for the safety population (all randomized patients who received at least 1 confirmed dose of trial drug) with no imputation for missing data. Analyses were conducted for ATMOS-1 (prespecified), ATMOS-2 (prespecified), and pooled ATMOS-1 and ATMOS-2 (post hoc).

RESULTS

Patient disposition, demographics, and baseline characteristics

A total of 344 patients in ATMOS-1 and 353 patients in ATMOS-2 were randomized (Fig 2). In both trials, GT was well tolerated, with at least 90% of patients completing week 4. The most common reasons for discontinuation were TEAEs and withdrawn consent. Patient demographics were generally similar across treatment arms and trial sites (Table I). In ATMOS-1, GT-treated patients had higher mean sweat production at baseline than vehicle-treated patients did, whereas in ATMOS-2, GT-treated patients had lower mean sweat production than their vehicle-treated counterparts, though the standard deviation was large across arms in both trials. In ATMOS-1, a larger proportion of GT-treated patients had HDSS grade 4 than did vehicle-treated patients (41.9% vs 27.0%), whereas patients with HDSS grades 3 and 4 were more uniformly distributed across treatment arms in ATMOS-2.

Efficacy end points

In each trial, the ASDD/ASDD-C Item 2 responder rates were significantly higher for GT versus vehicle at week 4 (coprimary end point [$P < .001$ for both trials]) (Fig 3). At week 4, a statistically significant difference favoring GT for mean absolute CfB in sweat production was seen in ATMOS-2 (coprimary end point [$P < .001$]) but not in ATMOS-1 ($P = .065$) (Table II). The prespecified sensitivity analysis identified 1 analysis center in ATMOS-1 with extreme outlier data for gravimetric measurement of sweat, which was then excluded (14 patients [9 of whom received GT and 5 of whom received vehicle]); analysis of the remaining patients showed that at week 4 in ATMOS-1, the GT group (n = 220) had a greater reduction in gravimetrically measured sweat production than did the vehicle group (n = 110 [$P = .001$] (Table II). Significant improvement in ASDD/ASDD-C Item 2 responder rates at week 4 was also seen for GT versus vehicle in the sensitivity analysis of the ATMOS-1 population (53% vs 30% [$P < .001$]). Differences favoring GT in ASDD/ASDD-C Item 2 responder rates and mean absolute CfB in sweat production occurred as early as week 1 in both studies, with continued improvement through week 4 (Fig 3). Similar results

Table II. Change in sweat production to week 4

Change from baseline in sweat production[‡] (mg/5 min), mean ± SD (median)	ATMOS-1			ATMOS-2			Pooled		
	Vehicle (n = 115)	GT (n = 229)	*P* value[*]	Vehicle (n = 119)	GT (n = 234)	*P* value[*]	Vehicle (n = 234)	GT (n = 463)	*P* value[*,†]
Week 1	−58.0 ± 121.6 (−47.6)	−75.5 ± 269.8 (−69.3)	—	−56.8 ± 151.9 (−42.4)	−108.0 ± 142.3 (−71.5)	—	−57.4 ± 137.0 (−44.9)	−91.9 ± 205.3 (−70.4)	—
Week 2	−71.5 ± 114.4 (−53.2)	−85.7 ± 277.4 (−77.9)	—	−86.0 ± 139.7 (−56.8)	−111.4 ± 137.3 (−78.1)	—	−78.9 ± 127.3 (−55.0)	−98.7 ± 206.6 (−78.0)	—
Week 3	−90.8 ± 133.8 (−62.9)	−88.9 ± 283.0 (−75.6)	—	−85.6 ± 127.9 (−54.2)	−110.3 ± 135.7 (−73.9)	—	−88.1 ± 130.8 (−58.5)	−99.7 ± 208.6 (−74.7)	—
Week 4 (coprimary end point)	−91.9 ± 128.0 (−65.8)	−104.9 ± 284.9 (−80.8)		−92.2 ± 152.7 (−57.9)	−110.3 ± 131.2 (−78.8)		−92.1 ± 140.6 (−61.8)	−107.6 ± 207.2 (−79.8)	
Interquartile range	−105.7 to −27.7	−148.8 to −40.2		−121.9 to −21.2	−144.0 to −45.5		−113.9 to −24.4	−146.4 to −42.9	
LS mean ± SD	−100.3 (172.3)	−102.0 (176.1)	.065	−81.2 (66.7)	−115.4 (66.5)	**<.001**	−90.6 (129.3)	−108.8 (131.4)	**<.001**
Week 4 prespecified sensitivity analysis excluding extreme outlier data[*,§]	*−90.6 ± 129.2 (−65.1) (n = 110)*	*−96.2 ± 125.5 (−82.0) (n = 220)*		—	—	—	—	—	—
Interquartile range	−104.0 to −23.6	−149.1 to −41.4		—	—	—	—	—	—
LS mean ± SD	−88.1 (95.7)	−100.6 (98.2)	**.001**	—	—	—	—	—	—

Boldface indicates statistical significance.

GT, Glycopyrronium tosylate; *LS*, least squares; *SD*, standard deviation.

*GT vs vehicle with use of a ranked analysis of covariance model in which treatment group and analysis center are used as factors and baseline sweat production is used as the covariant (intent-to-treat population, Markov chain Monte Carlo method used for multiple imputation of missing data).

†*P* value for the pooled analysis is nominal.

‡Gravimetrically measured average of the right and left axillae.

§As outlined in the prespecified statistical analysis plan, we conducted a sensitivity analysis that led to exclusion of an analysis center with extreme outlier data for the gravimetric measurement of sweat. This analysis center included 14 patients (9 received topical GT and 5 received vehicle).

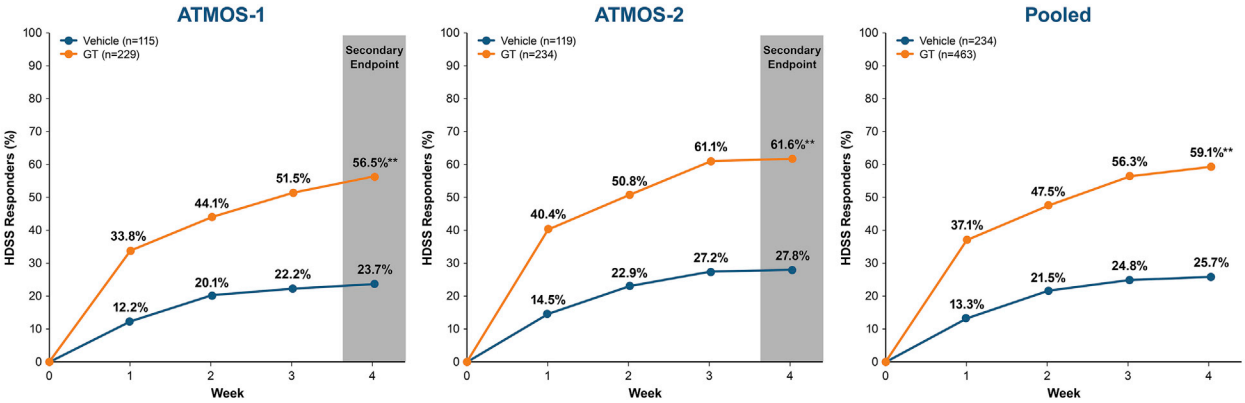

Fig 4. Hyperhidrosis: proportion of patients with at least a 2-grade improvement from baseline on the Hyperhidrosis Disease Severity Scale. Data are for the intent-to-treat population. The Markov chain Monte Carlo method was used for multiple imputation of missing data; *P* value was calculated for glycopyrronium tosylate (GT) versus vehicle with use of the Cochran-Mantel-Haenszel test stratified by analysis center at week 4 (*P* values were calculated only for week 4; *P* values for the pooled analysis are nominal). $^{**}P < .001$.

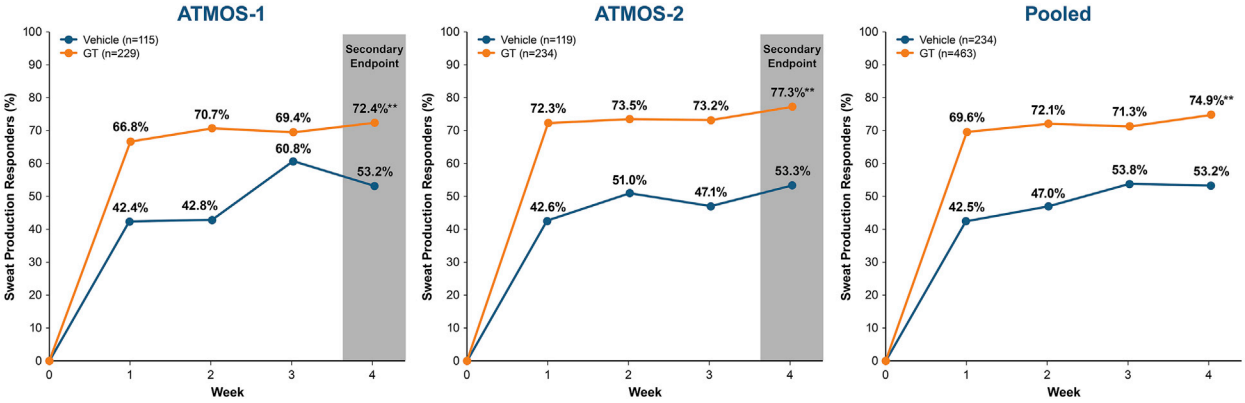

Fig 5. Hyperhidrosis: proportion of patients with a 50% or greater reduction from baseline in sweat production. Sweat production was measured gravimetrically (average of both axillae). Data are for the intent-to-treat population. The Markov chain Monte Carlo method was used for multiple imputation of missing data. *P* value was calculated for glycopyrronium tosylate (GT) versus vehicle with use of the Cochran-Mantel-Haenszel test stratified by analysis center at week 4 (*P* values were calculated only for week 4; *P* values for the pooled analysis are nominal). $^{**}P < .001$.

were observed in the pooled analysis (Fig 3 and Table II).

With regard to HDSS score and sweat production, the proportion of responders at week 4 was significantly higher for GT versus vehicle ($P < .001$ for each outcome in both trials), with a difference occurring as early as week 1; this pattern was mirrored in the pooled analysis (Figs 4 and 5).

Safety

The incidence of TEAEs was similar across the trials, and the majority were mild or moderate and transient, and they led to discontinuation only infrequently (<4% in each arm in each trial) (Table III). In ATMOS-1, 33.9% and 15.8% of TEAEs were considered treatment related in the GT and vehicle groups, respectively, which was similar to what was observed in ATMOS-2 (rates of 44.0% and 16.9%). The most frequently reported anticholinergic-related TEAEs were dry mouth and mydriasis (Table III). TEAEs of special interest occurred in 11.0% of GT-treated patients in ATMOS-1 and 15.5% of GT-treated patients in ATMOS-2 (no vehicle-treated patients reported a TEAE of special interest in either trial); they included blurry vision (3.5% and 3.4%), mydriasis (6.6% and 6.9%), and symptoms associated with urinary hesitancy and/or retention (3.1% and 8.2%).

Table III. Safety overview and TEAEs through week 4 (safety population)

Indicator	ATMOS-1		ATMOS-2		Pooled	
	Vehicle, n (%) (n = 114)	GT, n (%) (n = 227)	Vehicle, n (%) (n = 118)	GT, n (%) (n = 232)	Vehicle, n (%) (n = 232)	GT, n (%) (n = 459)
TEAE						
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[*,†]	0	1 (0.4)	0	1 (0.4)	0	2 (0.4)
Discontinuations due to a TEAE	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						
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)
Common TEAEs reported in ≥5% of patients in either treatment arm in pooled population						
Dry mouth[‡]	4 (3.5)	43 (18.9)	9 (7.6)	68 (29.3)	13 (5.6)	111 (24.2)
Application site pain	11 (9.6)	20 (8.8)	11 (9.3)	20 (8.6)	22 (9.5)	40 (8.7)
Mydriasis[‡,§]	0	15 (6.6)	0	16 (6.9)	0	31 (6.8)
Oropharyngeal pain	2 (1.8)	9 (4.0)	1 (0.8)	17 (7.3)	3 (1.3)	26 (5.7)
Headache	3 (2.6)	10 (4.4)	2 (1.7)	13 (5.6)	5 (2.2)	23 (5.0)
Anticholinergic TEAEs reported in >2% of patients in either treatment arm in ATMOS-1 or ATMOS-2						
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)
Local skin reactions[‖]	n = 114	n = 224	n = 117	n = 230	n = 231	n = 454
Any	32 (28.1)	73 (32.6)	38 (32.5)	67 (29.1)	70 (30.3)	140 (30.8)
Maximum postbaseline severity						
Mild	28 (24.6)	62 (27.7)	33 (28.2)	59 (25.7)	61 (26.4)	121 (26.7)
Moderate	2 (1.8)	11 (4.9)	5 (4.3)	7 (3.0)	7 (3.0)	18 (4.0)
Severe	2 (1.8)	0	0	1 (0.4)	2 (0.9)	1 (0.2)
Edema	3 (2.6)	6 (2.7)	3 (2.6)	7 (3.0)	6 (2.6)	13 (2.9)
Erythema	18 (15.8)	41 (18.3)	21 (17.9)	36 (15.7)	39 (16.9)	77 (17.0)
Dryness	2 (1.8)	6 (2.7)	1 (0.9)	10 (4.3)	3 (1.3)	16 (3.5)
Scaling	3 (2.6)	8 (3.6)	0	5 (2.2)	3 (1.3)	13 (2.9)
Burning/stinging	14 (12.3)	31 (13.8)	25 (21.4)	33 (14.3)	39 (16.9)	64 (14.1)
Pruritus	9 (7.9)	17 (7.6)	5 (4.3)	20 (8.7)	14 (6.1)	37 (8.1)

GT, Glycopyrronium tosylate; *TEAE*, treatment-emergent adverse event.

*In ATMOS-1, serious TEAEs refers to moderate unilateral mydriasis considered related to the study drug; in ATMOS-2, serious TEAEs refers to moderate dehydration considered not related to the study drug.

†Serious TEAEs are those that resulted in death, were immediately life-threatening, required inpatient hospitalization, resulted in persistent or significant disability, or were judged to require medical/surgical attention to avoid any of the aforementioned outcomes.

‡Mydriasis and dry mouth appear twice in this table because they meet the criteria for common adverse events and are associated with use of an anticholinergic.

§Most mydriasis events were unilateral: in ATMOS-1, 13 of 15; in ATMOS-2, 10 of 16; and pooled, 23 of 31.

‖Local skin reactions observed at study visits were not recorded as adverse events unless scored as severe, whereas those experienced between study visits were recorded as adverse events regardless of severity. Local skin reaction data are presented for patients in the safety population who had an assessment of postbaseline local skin reaction.

Among the 6.8% of pooled GT-treated patients experiencing mydriasis, most events were unilateral (ATMOS-1, 86.7% [13 of 15 events]; ATMOS-2, 62.5% [10 of 16 events]), whereas most blurred vision events were bilateral (ATMOS-1, 50.0% [4 of 8]; ATMOS-2, 87.5% [7 of 8]); treatment was not discontinued in most cases. The onset of common TEAEs and TEAEs of special interest occurred mainly

in the first week of treatment and decreased thereafter (Supplemental Table I; available at http://www.jaad.org). Two serious TEAEs were reported in the pooled population, both of which were in groups treated with GT (moderate unilateral mydriasis [considered treatment related] in ATMOS-1 and moderate dehydration [considered treatment unrelated] in ATMOS-2).

No notable differences were observed between the GT and vehicle treatment groups with respect to physical examination results, laboratory findings, vital signs, or electrocardiogram results. Most patients had no LSRs; when LSRs did occur, the rates were comparable in the GT and vehicle arms and the events were predominantly mild, with discontinuation occurring in only 1 patient (a patient who was treated with GT and experienced pruritus) (Table III).

DISCUSSION

Individual and pooled data from these 2 phase 3 trials demonstrate that GT treatment over 4 weeks significantly reduced severity of sweating and sweat production as assessed by the coprimary end points of the ASDD/ASDD-C Item 2 responder rate and mean absolute CfB in gravimetric measurement of sweat production, respectively. These improvements occurred as early as week 1 and were consistent with clinically meaningful reductions in axillary sweating soon after initiation of treatment. The results in terms of HDSS score were similar to those obtained with use of the ASDD/ASDD-C, with significantly greater responder rates for GT versus vehicle at week 4 and improvement beginning at week 1.

Most TEAEs were transient, reversible, and (if needed) managed by temporarily withholding trial drug or applying trial drug every other day. TEAEs generally did not recur upon re-challenge. As a rule, LSRs were mild-to-moderate in severity. Topical application of GT is intended to minimize but not completely eliminate anticholinergic effects from systemic exposure. The GT-treated patients experienced more TEAEs throughout the 4-week trial than the vehicle-treated patients did, suggesting that some patients may absorb enough drug to produce anticholinergic side effects. Because this drug is applied topically, patients who do not wash their hands following application may experience events that are also a result of inadvertent transfer of the drug from the hands to areas of the body such as the eyes. Unilateral ophthalmologic events of mydriasis and blurred vision were likely due to local exposure of the eye to the drug, whereas events such as dry mouth and urinary hesitation were likely due to systemic exposure.

The effect of vehicle in these trials, though much smaller than the effect of GT, has been observed in other dermatology trials[17,18] and indicates the importance of using a matching vehicle comparator in hyperhidrosis trials and appropriate excipients for GT. Limitations to consider when interpreting data include the relatively short duration of the trial compared with the chronicity of hyperhidrosis; however, long-term safety data for the open-label extension of these trials have been reported, and the results are consistent with those observed in the current trials.[19] Another limitation is the measurement of sweat production over a 5-minute period once-a-week. Although gravimetric tests were conducted in a temperature- and humidity-regulated clinic room, the sweating of patients with hyperhidrosis can be episodic and can vary depending on time of day, emotional stimuli, and/or daily activities.[20] The other coprimary end point in these trials was the responder rate on a PRO measure, namely, the ASDD/ASDD-C Item 2 (severity of sweating), which was rigorously developed and validated with patient input, consultation with clinical experts, and consideration of current regulatory standards.[12] In both trials, the ASDD/ASDD-C Item 2 responder rates were significantly higher for GT than for vehicle; the rates improved over time, and they were remarkably consistent between the 2 trials.

In conclusion, topically applied GT significantly reduced severity of sweating and sweat production by week 4, which is consistent with a clinically meaningful benefit, and differences between treatment groups were reported as early as week 1. Daily application of GT over 4 weeks was generally well tolerated; most TEAEs were in line with the expected anticholinergic effects and were mild or moderate and transitory, leading to discontinuation only infrequently. These trials included additional PRO measures and a post hoc analysis comparing pediatric (≤16 years) and older patients (>16 years), which showed no impact of age on primary efficacy outcomes.[21,22] Topical, once-daily GT may provide a noninvasive, well-tolerated treatment option for primary axillary hyperhidrosis.

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Axillary Sweating Daily Diary (ASDD)[a,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)[a,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

Supplemental Fig 1. Axillary hyperhidrosis patient measures. The Axillary Sweating Daily Diary/Axillary Sweating Daily Diary-Children Item 2 is a validated patient-reported outcome measure.

Supplemental Table I. Common TEAEs and TEAEs of Special Interest by Onset Week in the Pooled Population

	Baseline to week 1		Week 1 to week 2		Week 2 to week 3		Week 3 to week 4	
TEAE	Vehicle (n = 232), n (%)	GT (n = 459), n (%)	Vehicle (n = 232), n (%)	GT (n = 459), n (%)	Vehicle (n = 232), n (%)	GT (n = 459), n (%)	Vehicle (n = 232), n (%)	GT (n = 459), n (%)
Common TEAEs (≥5% of patients in either treatment arm in pooled population)								
Dry mouth	10 (4.3)	86 (18.7)	1 (0.4)	21 (4.6)	2 (0.9)	11 (2.4)	0	8 (1.7)
Application site pain	16 (6.9)	27 (5.9)	3 (1.3)	9 (2.0)	1 (0.4)	3 (0.7)	3 (1.3)	1 (0.2)
Mydriasis	0	17 (3.7)	0	9 (2.0)	0	4 (0.9)	0	2 (0.4)
Oropharyngeal pain	0	18 (3.9)	0	5 (1.1)	3 (1.3)	1 (0.2)	0	2 (0.4)
Headache	1 (0.4)	12 (2.6)	4 (1.7)	6 (1.3)	0	4 (0.9)	0	1 (0.2)
TEAEs of special interest								
Mydriasis	0	17 (3.7)	0	9 (2.0)	0	4 (0.9)	0	2 (0.4)
Urinary hesitation	0	12 (2.6)	0	1 (0.2)	0	1 (0.2)	0	2 (0.4)
Vision blurred	0	6 (1.3)	0	3 (0.7)	0	5 (1.1)	0	2 (0.4)
Urinary retention	0	5 (1.1)	0	1 (0.2)	0	0	0	1 (0.2)
Urine flow decreased	0	2 (0.4)	0	2 (0.4)	0	0	0	0
Nocturia	0	1 (0.2)	0	0	0	0	0	0
Pollakiuria	0	1 (0.2)	0	0	0	0	0	0

Patients were counted once per preferred term and onset week. TEAEs of special interest were protocol-defined on the basis of the association with systemic anticholinergic compounds and were blurry vision, mydriasis, and symptoms associated with urinary hesitancy/retention.

GT, Glycopyrronium tosylate; *TEAEs*, treatment-emergent adverse events.