# Glycopyrronium Tosylate for the Treatment of Primary Axillary Hyperhidrosis: Pediatric Subgroup Analyses from the ATMOS-1 and ATMOS-2 Phase 3 Randomized Controlled Trials

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## Author Disclosures

- **Adelaide A. Hebert**: Consultant for Dermira, Inc.; employee of the UTHealth McGovern Medical School, Houston, which received compensation from Dermira, Inc. for study participation
- **Dee Anna Glaser**: Consultant and investigator for Dermira, Inc.
- **Lawrence Green**: Investigator for Brickell, Inc; advisory board member and investigator for Dermira, Inc.
- **William P. Werschler**: Consultant and investigator for Dermira, Inc.
- **Douglass W. Forsha**: Investigator for Jordan Valley Dermatology and Research Center
- **Janice Drew**: Employee of Dermira, Inc.
- **Ramanan Gopalan**: Employee of Dermira, Inc.
- **David M. Pariser**: Consultant and investigator for Dermira, Inc.

## Background

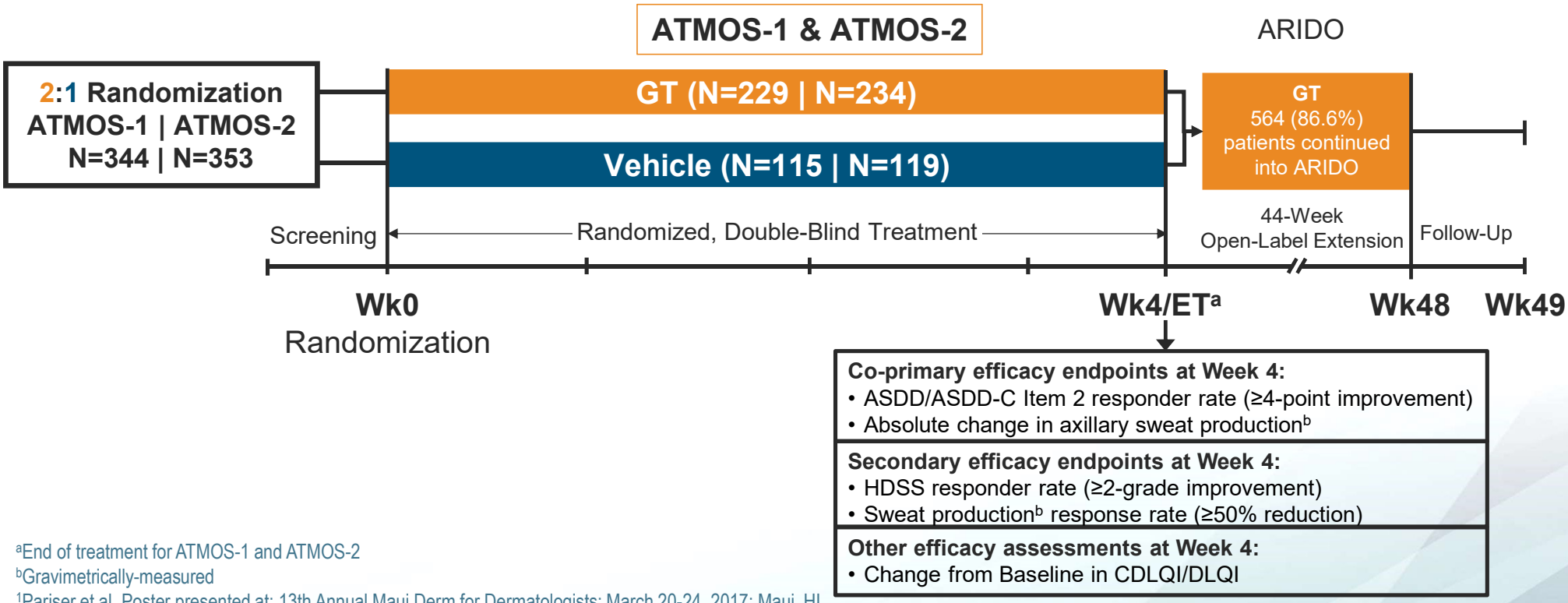
- Hyperhidrosis affects ~4.8% of the US population (15.3 million),[1] with an impact on quality of life comparable to, or greater than, psoriasis or eczema[2]
  - In an online survey, 17.1% of US teens reported experiencing excessive sweating[3]
- Hyperhidrosis is largely undertreated and underdiagnosed, particularly among pediatric patients[1,4]
- Glycopyrronium tosylate (GT) is a topically-applied, once-daily anticholinergic being developed for treatment of primary axillary hyperhidrosis, including pediatric patients (≥9 years)
- GT has improved disease severity, reduced sweat production, and improved quality of life in patients evaluated in two randomized, pivotal phase 3 studies for primary axillary hyperhidrosis (ATMOS-1 [NCT02530281] and ATMOS-2 [NCT02530294])[5]

**OBJECTIVE: Evaluate the response of pediatric patients (≥9 to ≤16 years) versus the older subgroup (>16 years) to GT at Week 4 in a pooled post hoc analysis of ATMOS-1 and ATMOS-2**

[1]Doolittle et al. Arch Dermatol Res. 2016; 308 (10):743-9; [2]Naumann et al. Value Health. 2003;6(3):242; [3]Hebert et al. Oral presentation at: 75th Annual American Academy of Dermatology; March 3-7; Orlando, FL; [4]Gelbard et al. Pediatr Dermatol. 2008;25(6):591-8; [5]Pariser et al. Poster presented at: 13th Annual Maui Derm for Dermatologists; March 20-24, 2017; Maui, HI
GT, topical glycopyrronium tosylate

# Study Design

- ATMOS-1 (sites in the US and Germany) and ATMOS-2 (US sites only) were randomized, double-blind, parallel-group, vehicle-controlled, 4-week pivotal phase 3 studies[1]




[a]End of treatment for ATMOS-1 and ATMOS-2
[b]Gravimetrically-measured
[1]Pariser et al. Poster presented at: 13th Annual Maui Derm for Dermatologists; March 20-24, 2017; Maui, HI
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

# Axillary Sweating Daily Diary (ASDD): Co-primary endpoint

- The 4-item ASDD (patients ≥9 to <16 years completed the 2-item ASDD-Children [ASDD-C]) is a component of the Axillary Hyperhidrosis Patient Measures (AHPM), which consists of three patient-reported outcome measures developed according to current regulatory standards for use in clinical trials
- ASDD/ASDD-C axillary sweating severity item (Item 2) was validated for use as an endpoint in clinical trials

| Axillary Sweating Daily Diary (ASDD)[a] | |
|---|---|
| *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.*<br>*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?<br>Yes/No<br>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?<br>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?<br>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?<br>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)[b] | |
|---|---|
| *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.*<br>*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?<br>Yes/No<br>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?<br>0 (no sweating at all) to 10 (worst possible sweating) |

[a]For use in patients ≥16 years of age
[b]For use in patients ≥9 to <16 years of age
Glaser et al. Poster presentation at: EADV (2017). Abstract 3655

# Inclusion/Exclusion Criteria

## Inclusion:

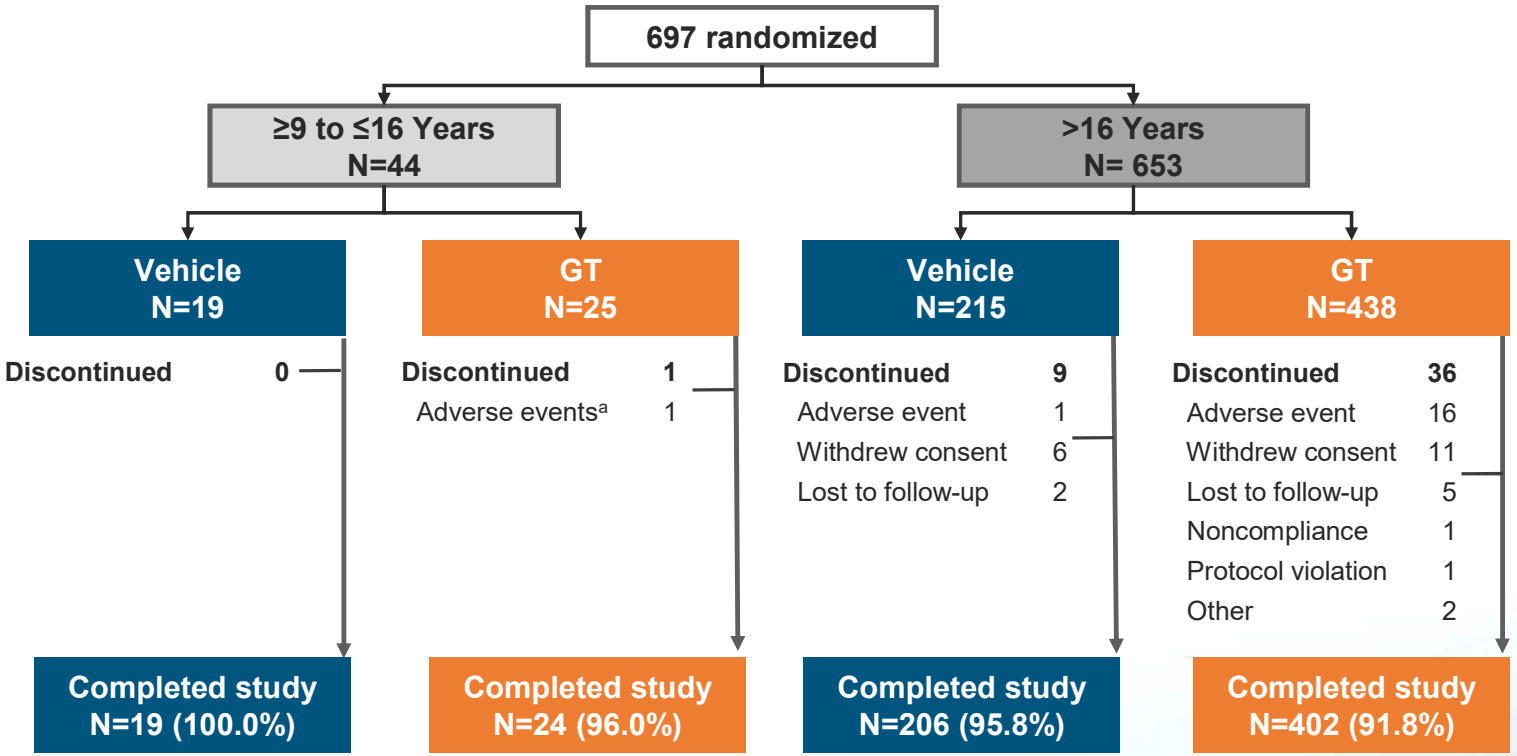
- ≥9 years of age
  - US sites recruited patients ≥9 years
  - Germany sites only recruited patients ≥18 years (ATMOS-1 only)
- Primary axillary hyperhidrosis for ≥6 months, with:
  - Gravimetrically-measured sweat production ≥50 mg/5 min in each axilla
  - Axillary Sweating Daily Diary (ASDD/ASDD-Children [ASDD-C]) axillary sweating severity item (Item 2)[1] score ≥4
  - Hyperhidrosis Disease Severity Scale (HDSS) ≥3

## Exclusion:

- 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 within 1 year for axillary hyperhidrosis
- Axillary use of nonprescription antiperspirants within 1 week or prescription antiperspirants 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

[1]Glaser et al. Poster presented at: 13th Maui Derm for Dermatologists Congress; March 20-24, 2017; Maui, HI

# Pediatric Subgroup Had High Completion Rates




[a]Patient had five drug-related events that led to discontinuation: mild vision blurred (bilateral), severe mydriasis (bilateral), severe dry mouth, severe urinary retention, and severe anhidrosis

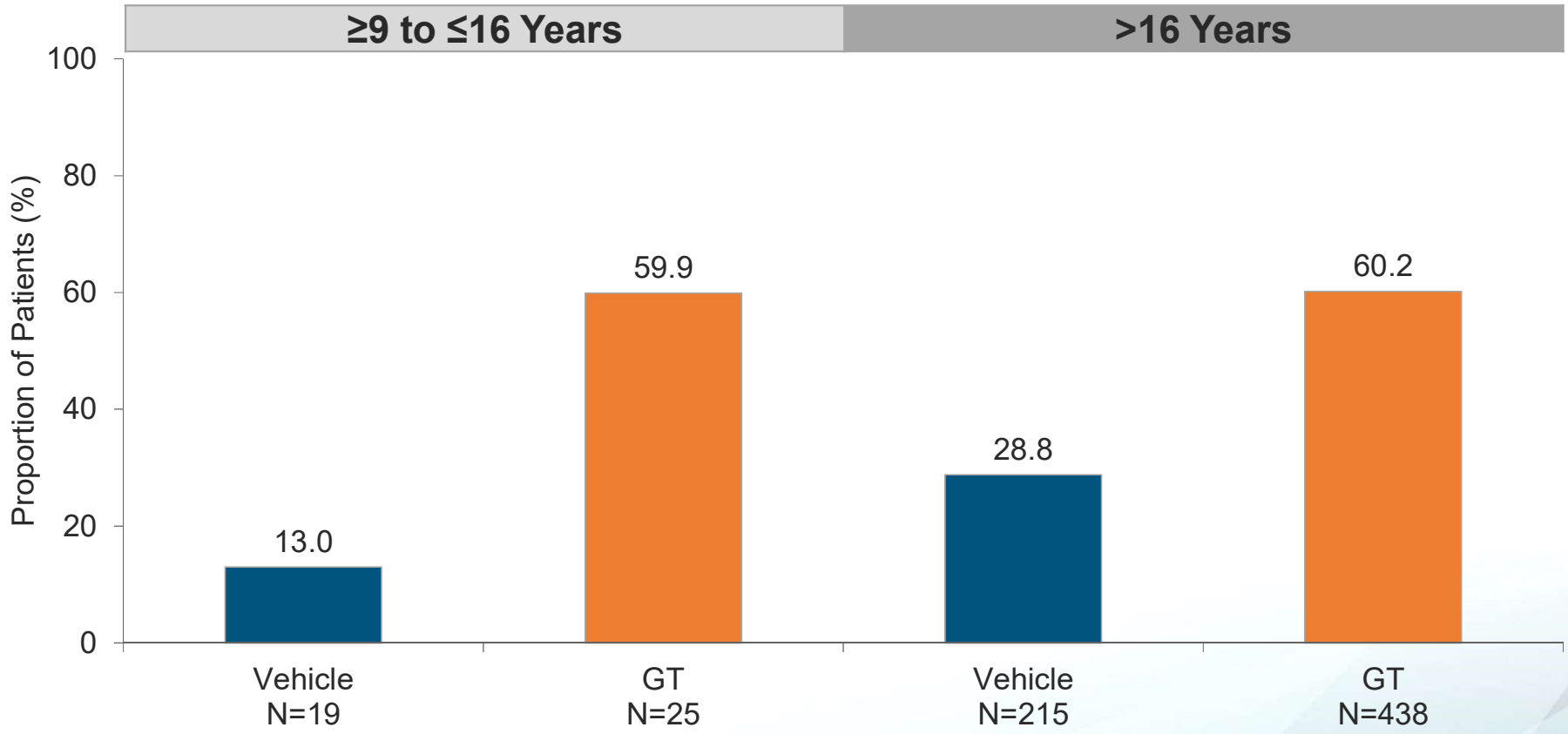
GT, topical glycopyrronium tosylate

# Patient Demographics and Baseline Disease Characteristics

| | ≥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] |

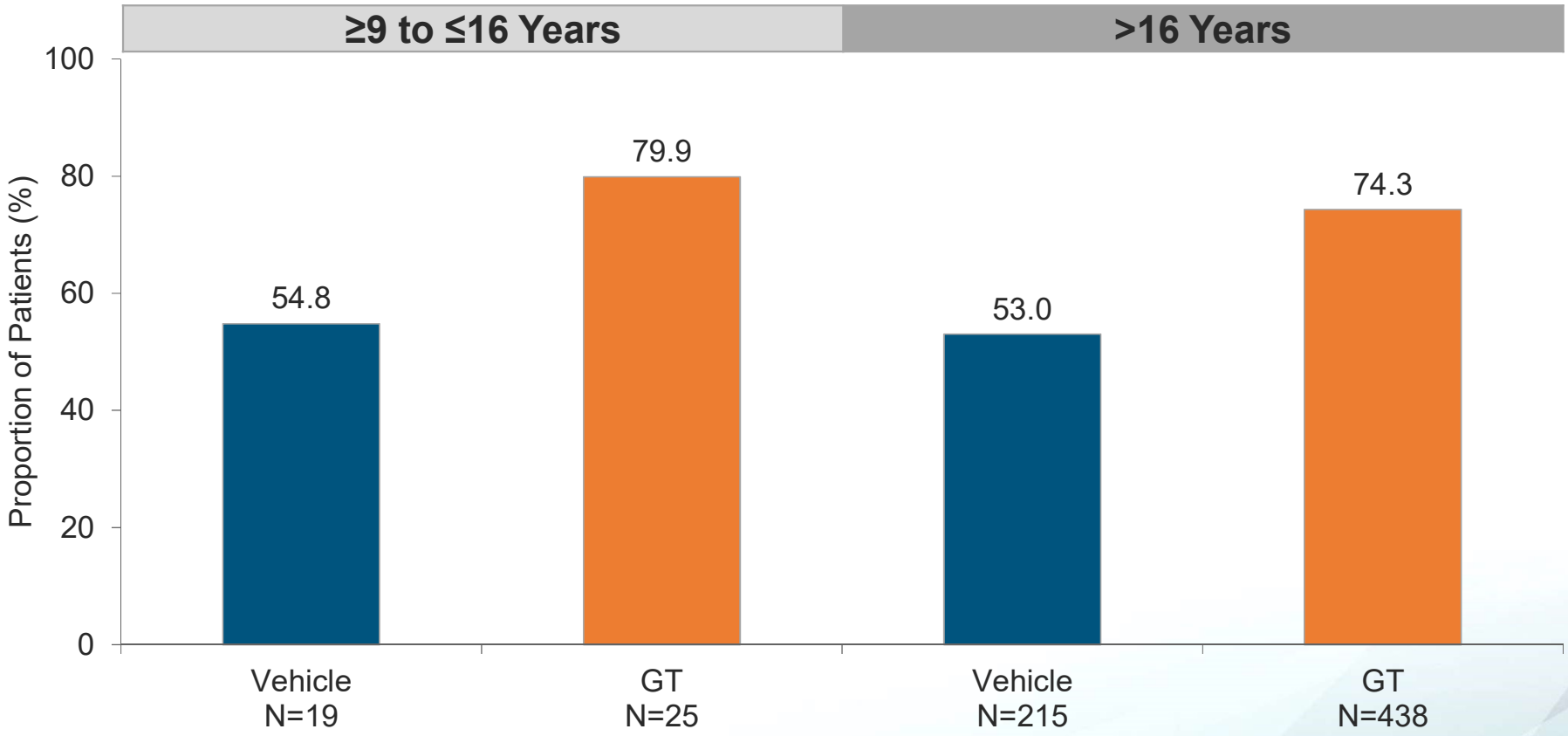
[a]Gravimetrically-measured average from the left and right axillae
[b]N=24 for GT group ≥9 to ≤16 years of age
[c]Patients ≥9 to ≤16 years of age were administered the CDLQI and patients >16 years of age were administered the DLQI
Intent-to-treat (ITT) population
ASDD, Axillary Sweating Daily Diary; 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

# ASDD/ASDD-C Item 2 Responder Rates (≥4-Point Improvement) at Week 4 Were Similar Between Pediatric and Older Subgroups



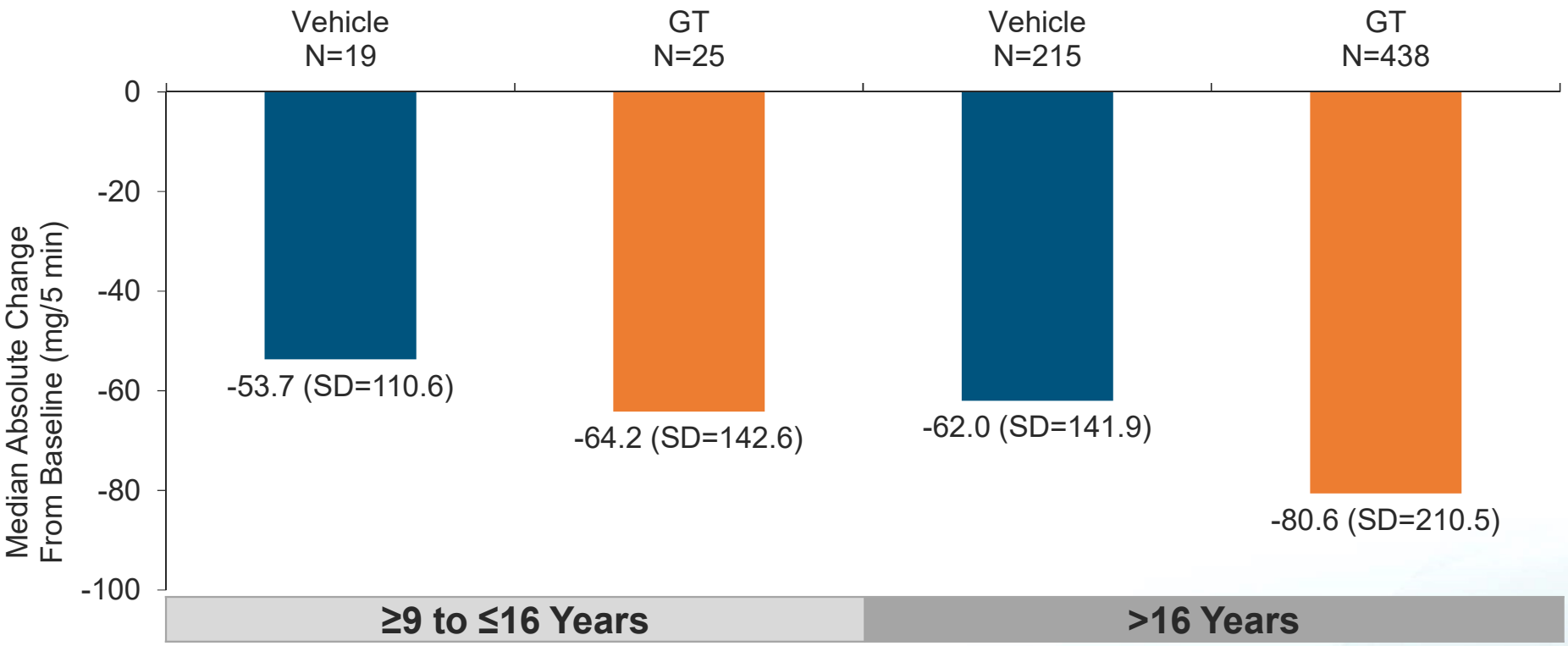

Pooled ATMOS-1/ATMOS-2 data; intent-to-treat (ITT) population
P-values were not calculated for this post hoc analysis; multiple imputation (MCMC) was used to impute missing values
ASDD, Axillary Sweating Daily Diary; ASDD-C, ASDD-Children; GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo

# Proportion of Patients With ≥50% Reduction in Sweat Production[a] at Week 4 Was Similar Between Pediatric and Older Subgroups



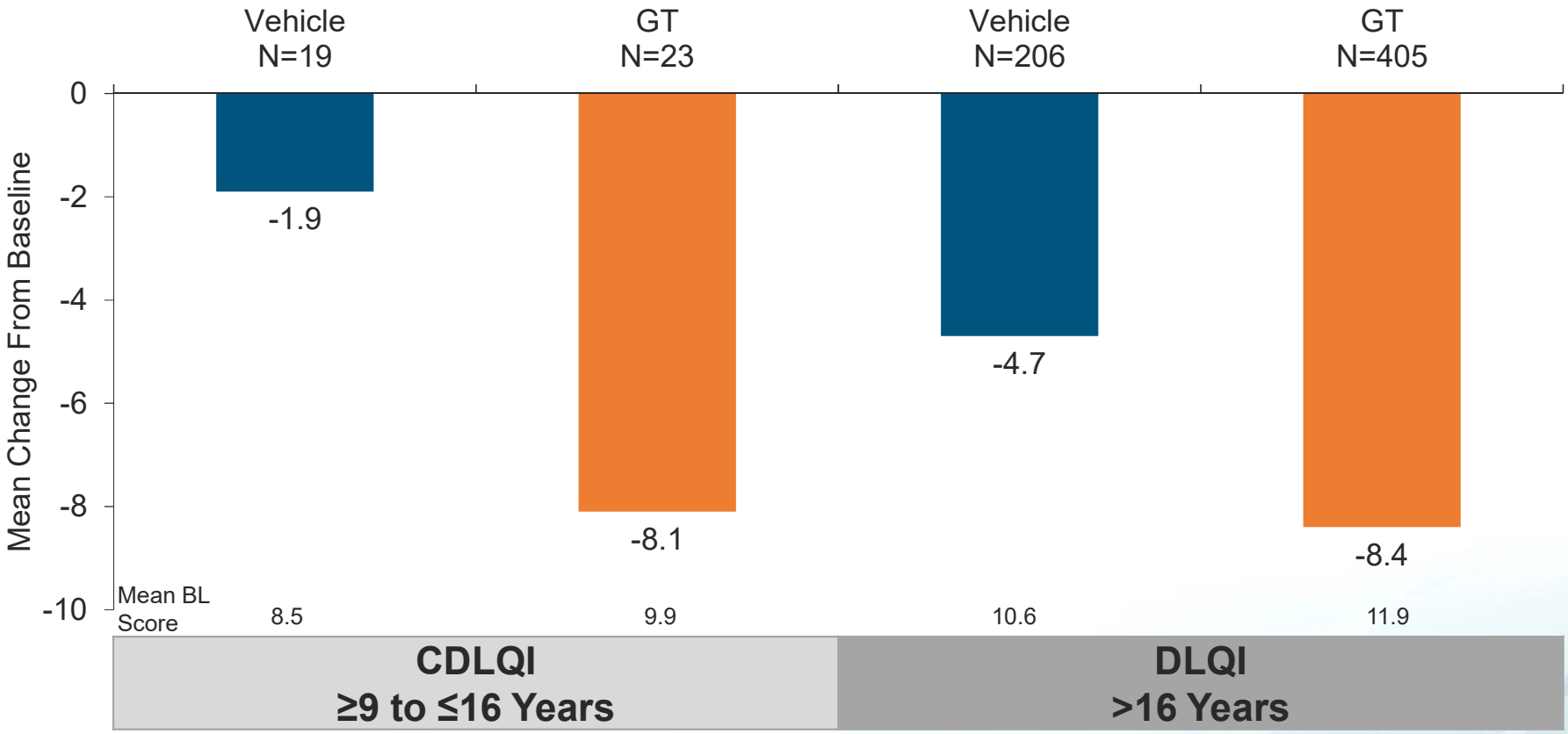

[a]Gravimetrically-measured average from the left and right axillae
Pooled ATMOS-1/ATMOS-2 data; intent-to-treat (ITT) population
P-values were not calculated for this post hoc analysis; multiple imputation (MCMC) was used to impute missing values
GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo

# Median Absolute Change in Sweat Production[a] at Week 4 Was Greater for GT- Versus Vehicle-Treated Patients in Both Subgroups




[a]Gravimetrically-measured average from the left and right axillae
Pooled ATMOS-1/ATMOS-2 data; intent-to-treat (ITT) population
Data labels show median (standard deviation)
P-values were not calculated for this post hoc analysis; multiple imputation (MCMC) was used to impute missing values
GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo; SD, standard deviation

# Improvements in Quality of Life With GT Were Similar Between Pediatric and Older Subgroups




Pooled ATMOS-1/ATMOS-2 data; intent-to-treat (ITT) population
No imputation of missing values
BL, Baseline; CDLQI, children's DLQI; DLQI, Dermatology Life Quality Index; GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo

# Pediatric and Older Subgroups Demonstrated Similar Safety Profiles

| | ≥9 to ≤16 Years | | >16 Years | |
|---|---|---|---|---|
| n[a] (%) | Vehicle N=19 | GT N=25 | Vehicle N=213 | GT N=434 |
| Any TEAE | 2 (10.5) | 11 (44.0) | 73 (34.3) | 246 (56.7) |
| Any Serious TEAE | 0 | 0 | 0 | 2 ( 0.5)[b] |
| Deaths | 0 | 0 | 0 | 0 |
| Discontinuation due to TEAE | 0 | 1 ( 4.0) | 1 ( 0.5) | 17 ( 3.9) |
| TEAE by intensity | | | | |
| Mild | 2 (10.5) | 6 (24.0) | 51 (23.9) | 164 (37.8) |
| Moderate | 0 | 4 (16.0) | 22 (10.3) | 79 (18.2) |
| Severe | 0 | 1 ( 4.0) | 0 | 3 ( 0.7) |
| TEAEs >5% in either treatment group | | | | |
| Nausea | 0 | 2 ( 8.0) | 0 | 4 ( 0.9) |
| Application site pain | 1 ( 5.3) | 2 ( 8.0) | 21 ( 9.9) | 38 ( 8.8) |
| Pain | 1 ( 5.3) | 0 | 0 | 1 ( 0.2) |
| Influenza | 1 ( 5.3) | 0 | 2 ( 0.9) | 3 ( 0.7) |
| Headache | 0 | 1 ( 4.0) | 5 ( 2.3) | 22 ( 5.1) |
| Oropharyngeal pain | 0 | 2 ( 8.0) | 3 ( 1.4) | 24 ( 5.5) |
| Epistaxis | 0 | 2 ( 8.0) | 1 ( 0.5) | 3 ( 0.7) |

[a]Numbers in table represent the number of patients reporting ≥1 TEAE, not number of events
[b]ATMOS-1: moderate unilateral mydriasis, considered related to study drug (led to discontinuation); ATMOS-2: moderate dehydration, considered not related to study drug (did not lead to discontinuation)
Pooled ATMOS-1/ATMOS-2 data; safety population
GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

# Pre-specified Anticholinergic TEAEs of Interest Reported in >2% of Patients Were Similar Between Subgroups

| | ≥9 to ≤16 Years | | >16 Years | |
|---|---|---|---|---|
| n[a] (%) | Vehicle N=19 | GT N=25 | Vehicle N=213 | GT N=434 |
| **Mydriasis** | 0 | 4 (16.0)[b] | 0 | 27 ( 6.2)[c] |
| **Vision blurred** | 0 | 3 (12.0) | 0 | 13 ( 3.0) |
| **Dry eye** | 0 | 1 ( 4.0) | 1 (0.5) | 10 ( 2.3) |
| **Dry mouth** | 0 | 6 (24.0) | 13 (6.1) | 105 (24.2) |
| **Urinary hesitation** | 0 | 0 | 0 | 16 ( 3.7) |
| **Urinary retention** | 0 | 1 ( 4.0) | 0 | 6 ( 1.4) |
| **Nasal dryness** | 0 | 1 ( 4.0) | 1 (0.5) | 11 ( 2.5) |

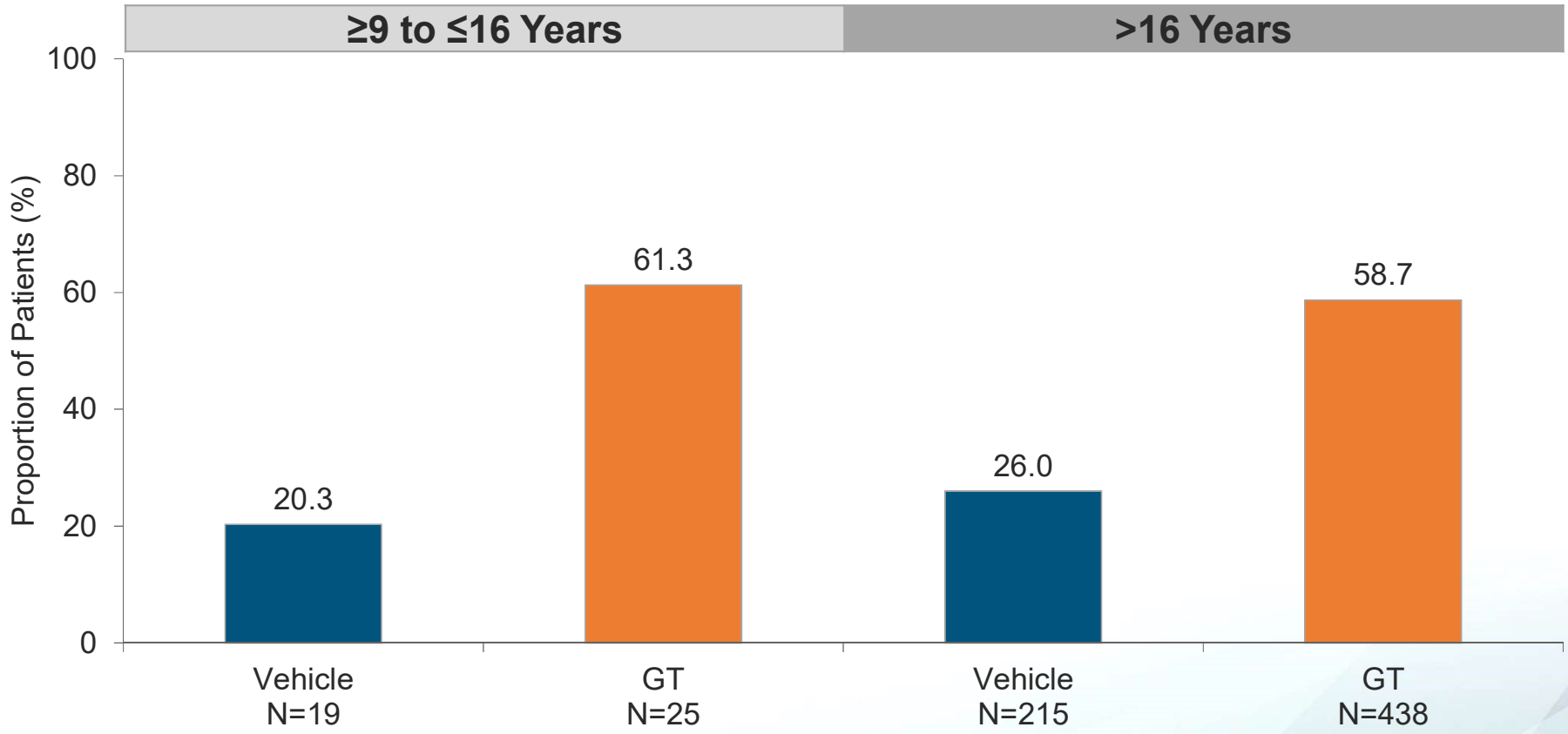
[a]Numbers in table represent the number of patients reporting ≥1 TEAE, not number of events
[b]1 patient reported a unilateral event; 3 patients reported bilateral events
[c]22 patients reported unilateral events; 5 patients reported bilateral events
Pooled ATMOS-1/ATMOS-2 data; safety population
GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

## Conclusions

- Hyperhidrosis is generally undertreated and underdiagnosed, especially among pediatric patients
- In this post hoc analysis of two large phase 3 trials, topically applied glycopyrronium tosylate improved disease severity, sweat production, and quality of life relative to vehicle, with similar findings in pediatric (≥9 to ≤16 years) and older (>16 years) patients
- Glycopyrronium tosylate was generally well tolerated in these studies, and TEAEs in pediatric patients were similar to those in patients >16 years and consistent with those seen with anticholinergic agents
  - Most anticholinergic TEAEs were mild, transient, and infrequently led to drug discontinuation
- Topical glycopyrronium tosylate treatment may provide a much needed treatment option for those with primary axillary hyperhidrosis, including pediatric patients

# Back-Up

# HDSS Responder Rates (≥2-Grade Improvement) at Week 4 Were Similar Among Pediatric Patients Versus the Older Subgroup




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, Axillary Sweating Daily Diary; ASDD-C, ASDD-Children; GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo

# AEs Leading to Discontinuation

| Subgroup / Treatment | Event | Relation to Study Drug | Study |
|---|---|---|---|
| Pediatric / GT | Vision blurred (bilateral), mydriasis (bilateral), urinary retention | Related | ATMOS-2 |
| Older / Vehicle | Laboratory test abnormal | Not related | ATMOS-1 |
| Older / GT | Urinary hesitation | Related | ATMOS-1 |
| Older / GT | Urine flow decreased | Not related | ATMOS-1 |
| Older / GT | Vision blurred (unilateral) and mydriasis (unilateral) | Related | ATMOS-1 |
| Older / GT | Pollakiuria; urinary hesitation | Not related; related | ATMOS-1 |
| Older / GT | Mydriasis (unilateral) | Related | ATMOS-1 |
| Older / GT | Fatigue | Not related | ATMOS-1 |
| Older / GT | Laboratory test abnormal | Not related | ATMOS-1 |
| Older / GT | Mydriasis (unilateral) | Related | ATMOS-1 |
| Older / GT | Dry mouth; palpitations | Related; unknown | ATMOS-2 |
| Older / GT | Dry mouth and constipation | Related | ATMOS-2 |
| Older / GT | Depressed level of consciousness | Unknown | ATMOS-2 |
| Older / GT | Urine flow decreased | Related | ATMOS-2 |
| Older / GT | Urinary retention | Related | ATMOS-2 |
| Older / GT | Urinary hesitation | Related | ATMOS-2 |
| Older / GT | Urinary retention | Related | ATMOS-2 |
| Older / GT | Urinary hesitation | Related | ATMOS-2 |

# Serious and Severe TEAEs

- Serious TEAEs:

| Subgroup / Treatment | Event | Relation to Study Drug | Outcome | Study |
|---|---|---|---|---|
| Older / GT | Moderate unilateral mydriasis | Related | Discontinuation | ATMOS-1 |
| Older / GT | Moderate dehydration | Not related | Completion | ATMOS-2 |

- Severe TEAEs:

| Subgroup / Treatment | Event | Relation to Study Drug | Outcome | Study |
|---|---|---|---|---|
| Pediatric / GT | Application site rash | Related | Completed | ATMOS-1 |
| Older / GT | Bilateral mydriasis, dry mouth, urinary retention, anhidrosis | Related | Discontinued | ATMOS-2 |
| Older / GT | Dry mouth | Related | Discontinued | ATMOS-2 |
| Older / GT | Dry mouth | Related | Completed | ATMOS-2 |