Open-Label Study (ARIDO) Evaluating Long-Term Safety of Topical Glycopyrronium Tosylate (GT) in Patients With Primary Axillary Hyperhidrosis

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INTRODUCTION

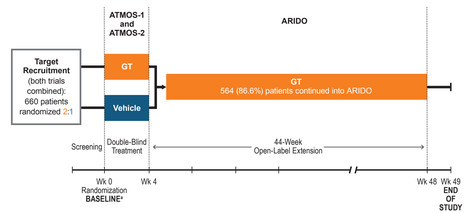
- Hyperhidrosis affects an estimated 4.8% of the US population, or approximately 15.3 million people,[1] and the impact of hyperhidrosis on quality of life is reported as comparable to, or greater than, psoriasis or eczema[2]
- Glycopyrronium tosylate (GT; formerly DRM04) is a topical cholinergic receptor antagonist being developed for the treatment of primary axillary hyperhidrosis in patients ≥9 years of age
- GT has been assessed in 2 replicate, randomized, double-blind, vehicle-controlled, pivotal phase 3 lead-in trials (ATMOS-1 and ATMOS-2)
  - GT was generally well tolerated and demonstrated clinically meaningful improvements in disease severity and reductions in sweat production through 4 weeks in these trials[3]
- ARIDO (NCT02553798) assessed the long-term safety of GT in a minimum of 100 patients with primary axillary hyperhidrosis treated for at least 12 months

METHODS

Study Design

- ARIDO was a 44-week, open-label extension of ATMOS-1 (NCT02530281) and ATMOS-2 (NCT02530294) (**Figure 1**)
- In ATMOS-1/ATMOS-2 patients with primary axillary hyperhidrosis were randomized 2:1 to GT (3.75% topical solution) or vehicle applied once daily to each axilla for 28 days (**Figure 1**)
- 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 weeks or until early termination, including patients terminated once the study objective of 100 patients receiving treatment for ≥12 months was achieved (**Figure 1**)
- Key inclusion criteria for ATMOS-1/ATMOS-2 were:
  - ≥9 years of age (patients <16 years were recruited only at US sites)
  - Primary axillary hyperhidrosis for ≥6 months
  - Gravimetrically-measured sweat production of ≥50 mg/5 min in each axilla
  - Axillary Sweating Daily Diary (ASDD; for patients ≥16 years of age) or ASDD-Children (ASDD-C; for patients <16 years of age) axillary sweating severity item (Item 2) 4 score ≥4 (0 to 10 numeric rating scale)
  - Hyperhidrosis Disease Severity Scale (HDSS) ≥3
- Key exclusion criteria for ATMOS-1/ATMOS-2 were:
  - 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
  - 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
  - Conditions that could be exacerbated by study medication

Figure 1. Study Design



*Baseline for ARIDO was Week 0 of ATMOS-1/ATMOS-2
GT, topical glycopyrronium tosylate; Wk, week

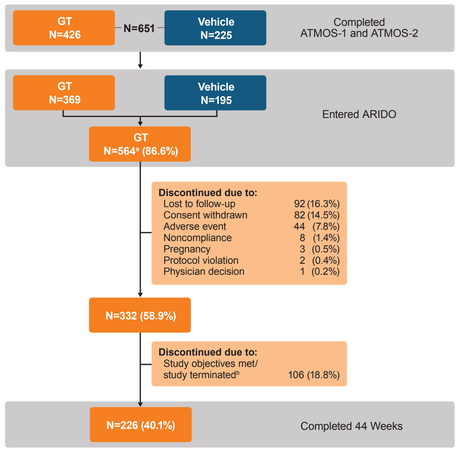
Assessments

- Primary objective was long-term safety
  - Safety was evaluated via treatment-emergent adverse events (TEAEs) through Week 45 (Week 44 + 1 week safety follow-up), local skin reactions (LSRs) through Week 44, laboratory testing, vital signs, and physical examinations
  - TEAEs are summarized overall from the first application of study drug in ARIDO to Week 45
- Descriptive efficacy assessments evaluated in ARIDO were an extension of the primary endpoints in ATMOS-1/ATMOS-2
  - Change from Baseline in ATMOS-1/ATMOS-2 in gravimetrically-measured sweat production at Week 44 (up to 48 weeks of GT)
  - Change from Baseline in ATMOS-1/ATMOS-2 in HDSS responder rate (≥2-grade improvement) at Week 44 (up to 48 weeks of GT)
- All safety and efficacy analyses were performed on the Safety Population (patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO)

RESULTS

- The majority of patients (86.6%; N=564) completing ATMOS-1/ATMOS-2 (369 patients [65.4%] had received GT, and 195 [34.6%] had received vehicle) continued into ARIDO (**Figure 2**)
- Of the patients enrolled in ARIDO, most patients were female (55.3%) and white (83.3%) with a mean age of 33.0 years and mean BMI of 27.3 kg/m^2 (**Table 1**)
- The trial was terminated, per protocol, once study objectives were reached
  - A total of 226 patients completed 44 weeks of treatment

Figure 2. Patient Disposition



[a]4 patients in ARIDO did not have a post-Baseline assessment and were therefore excluded from the Safety Population
[b]Sponsor terminated study early, per protocol, when study objective of 100 patients receiving treatment for at least 12 months was achieved
GT, topical glycopyrronium tosylate

Table 1. Demographics and Baseline[a] Disease Characteristics (Safety Population[b])

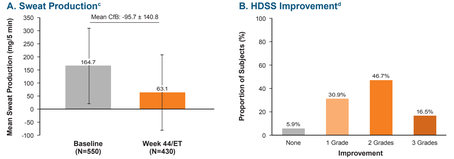
	GT (N=550)
Demographics	
Age (years), mean ± SD	33.0 ± 11.4
Age group, n (%) ≥16 years <16 years	 522 (94.9) 28 (5.1)
Female, n (%)	304 (55.3)
White, n (%)	458 (83.3)
BMI (kg/m^2), mean ± SD	27.3 ± 5.0
Baseline Disease Characteristics	
Sweat production (mg/5 min),[c] mean ± SD	164.7 ± 145.0
HDSS,[d,e] n (%) Grade 3 Grade 4	 348 (63.3) 201 (36.5)
Quality of Life DLQI,[f] mean ± SD CDLQI,[g] mean ± SD	 11.4 ± 5.9 8.9 ± 5.4

[a]Baseline in ATMOS-1/ATMOS-2
[b]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
[c]Gravimetrically-measured average from the left and right axillae
[d]HDSS ≥3 was an inclusion criteria
[e]N=549; 1 subject entered ATMOS-2 with HDSS=2, which was a protocol violation
[f]Patients >16 years of age
[g]Patients ≤16 years of age
BMI, body mass index; CDLQI, Children's DLQI; DLQI, Dermatology Life Quality Index; GT, topical glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; SD, standard deviation

Efficacy Assessments

- Through Week 44/ET in ARIDO (up to 48 weeks of GT), GT-treated patients continued to demonstrate improvements in efficacy measures, including sweat production and HDSS responder rate (**Figure 3**)
  - From Baseline in ATMOS-1/ATMOS-2 to Week 44/ET in ARIDO, mean sweat production decreased by 95.7 ± 140.8 mg/5 min, which was maintained from a decrease of 107.6 ± 207.2 mg/5 min in GT-treated patients after 4 weeks in ATMOS-1/ATMOS-2 (**Figure 3A**)
  - At Week 44/ET in ARIDO, HDSS responder rate (≥2-grade improvement) was 63.2%, a further improvement from 59.1% in GT-treated patients at Week 4 in ATMOS-1/ATMOS-2
    - HDSS grade improved by 1, 2, and 3 grades in 30.9%, 46.7%, and 16.5% of patients, respectively (**Figure 3B**)

Figure 3. Mean Sweat Production and HDSS Improvement From Baseline[a] to Week 44/ET (Safety Population[b])



[a]Baseline in ATMOS-1/ATMOS-2
[b]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
[c]Gravimetrically-measured average from the left and right axillae
[d]N=437
CfB, change from Baseline; ET, early termination; HDSS, Hyperhidrosis Disease Severity Scale

Safety Assessments

- After 44 weeks, 329 (59.8%) patients reported ≥1 TEAE, though most were mild or moderate in severity (**Table 2**)
- A total of 44 (8.0%) patients discontinued due to a TEAE and 7 (1.3%) reported ≥1 serious TEAE (**Table 2**)
- Prespecified anticholinergic TEAEs of interest were reported in 78 (14.2%) patients; most were mild or moderate in severity and were able to be managed by dose interruption (**Table 2**)
  - 37 patients reported 45 vision blurred events; 40 (88.9%) were bilateral
  - 29 patients reported 37 mydriasis events; 31 (83.8%) were unilateral
- Generally, TEAEs, including TEAEs prespecified as anticholinergic TEAEs of interest, did not increase over time with longer duration of exposure (**Table 3**)
- 179 (32.5%) of patients reported LSRs, which were typically mild or moderate in severity (**Figure 4**)
- There were no clinically meaningful changes in laboratory parameters or vital signs

Table 2. Summary of Treatment-Emergent Adverse Events From Baseline[a] to Week 45/ET (Safety Population[b])

	GT (N=550)
Any TEAE, n (%)	329 (59.8)
Any Serious TEAE, n (%)	7 (1.3)[c]
Discontinuation due to a TEAE, n (%)	44 (8.0)
Deaths, n (%)	0
Most frequently reported TEAEs (>5% patients), n (%)	
Dry mouth	93 (16.9)
Vision blurred	37 (6.7)
Application site pain	35 (6.4)
Nasopharyngitis	32 (5.8)
Mydriasis	29 (5.3)
Prespecified anticholinergic TEAEs of interest, n (%)	78 (14.2)
Vision blurred	37 (6.7)[d]
Mydriasis	29 (5.3)[e]
Urinary hesitation	23 (4.2)
Nocturia	2 (0.4)
Urine flow decreased	2 (0.4)
Hypermetropia	1 (0.2)
Pollakiuria	1 (0.2)
Pupils unequal	1 (0.2)
	Any TEAEs (N=329)
TEAEs by severity, n (%)	
Mild	148 (45.0)
Moderate	153 (46.5)
Severe	28 (8.5)
Relation to study drug, n (%)	
Not related	131 (39.8)
Related	198 (60.2)

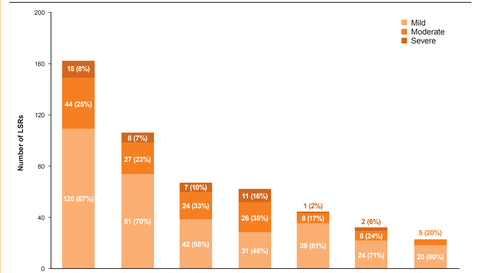
Numbers in table represent the number of patients reporting ≥1 TEAE, not number of events
[a]TEAEs are those with an onset after first application of study drug in ARIDO
[b]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
[c]Infectious colitis, affective disorder, suicide attempt, mydriasis, chest pain, concussion, diverticulitis
[d]37 patients reported 45 vision blurred events; 40 (88.9%) were bilateral
[e]29 patients reported 37 mydriasis events; 31 (83.8%) were unilateral
ET, early termination; GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

Table 3. Summary of Frequently Reported TEAEs and TEAEs of Special Interest (Safety Population[a])

	Duration of Exposure				
TEAEs, n (%)	0 to 4 weeks (N=550)	>4 to 8 weeks (N=537)	>8 to 20 weeks (N=479)	>24 to 36 weeks (N=417)	>36 weeks to ES (N=365)
Any TEAE	176 (32.0)	148 (27.6)	102 (21.3)	78 (18.7)	59 (16.2)
TEAEs reported in >5% of patients					
Dry mouth	59 (10.7)	23 (4.3)	19 (4.0)	15 (3.6)	5 (1.4)
Vision blurred	11 (2.0)	14 (2.6)	7 (1.5)	5 (1.2)	4 (1.1)
Application site pain	16 (2.9)	9 (1.7)	5 (1.0)	6 (1.4)	3 (0.8)
Nasopharyngitis	14 (2.5)	9 (1.7)	4 (0.8)	5 (1.2)	3 (0.8)
Mydriasis	8 (1.5)	8 (1.5)	9 (1.9)	5 (1.2)	2 (0.5)
Prespecified anticholinergic TEAEs of interest					
Vision blurred	11 (2.0)	14 (2.6)	7 (1.5)	5 (1.2)	4 (1.1)
Mydriasis	8 (1.5)	8 (1.5)	9 (1.9)	5 (1.2)	2 (0.5)
Urinary hesitation	14 (2.5)	4 (0.7)	4 (0.8)	2 (0.5)	1 (0.3)
Nocturia	2 (0.4)	0	0	0	0
Urine flow decreased	1 (0.2)	1 (0.2)	0	0	0
Hypermetropia	0	0	0	1 (0.2)	0
Pollakiuria	0	0	0	1 (0.2)	0
Pupils unequal	1 (0.2)	0	0	0	0

Numbers in table represent the number of patients reporting ≥1 TEAE, not number of events
TEAEs are those with an onset after first application of study drug in ARIDO
[a]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment on ARIDO
ES, end of study; GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event

Figure 4. Summary of Local Skin Reactions by Severity From Baseline[a] to Week 44/ET (Safety Population[b])



Patients were counted as having an LSR if any post-Baseline assessment was mild, moderate, or severe
[a]Baseline in ATMOS-1/ATMOS-2
[b]Patients receiving ≥1 dose of GT and having ≥1 post-Baseline assessment in ARIDO
ET, early termination; GT, topical glycopyrronium tosylate; LSR, local skin reaction

CONCLUSIONS

- Safety results were consistent with anticholinergic treatment and with the safety profile observed in prior GT studies,[3] with no new or unexpected findings
  - Most TEAEs were mild or moderate in severity and considered by the Investigator to be related to study drug
  - A low number of subjects discontinued due to a TEAE
  - While approximately one-third of patients reported local skin reactions, most were mild or moderate in severity
  - Incidence of TEAEs, including prespecified anticholinergic TEAEs of interest, did not increase with long-term treatment
- Efficacy measures obtained at the end of treatment in ARIDO indicated that subjects had maintained sweat production reduction and less bothersome sweating compared with Baseline in ATMOS-1/ATMOS-2
- GT was generally well tolerated and improvements in efficacy measures were maintained in patients with primary axillary hyperhidrosis when applied once daily to both axillae over a maximum of 48 weeks

References

1. Doolittle et al. *Arch Dermatol Res*. 2016;308(10):743-9. 2. Hamm. *Dermatol Clin*. 2014;32(4):467-76. 3. Pariser et al. Poster presented at: 25th European Academy of Dermatology and Venerology Congress; September 28-October 2, 2016; Vienna, Austria. 4. Glaser et al. Poster presented at: 13th Maui Derm for Dermatologists Congress; March 20-24, 2017; Maui, HI.

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Author Disclosures

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