Limited Systemic Exposure with Topical Glycopyrronium Tosylate across Multiple Studies in Healthy Volunteers and Patients with Primary Axillary Hyperhidrosis

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INTRODUCTION

- Hyperhidrosis is a chronic medical condition characterized by excess sweat production beyond that which is necessary to maintain thermal homeostasis, and affects an estimated 4.8% of the United States (US) population, or approximately 15.3 million people[1]
- Glycopyrronium tosylate (GT) is a topical anticholinergic approved in the US for treatment of primary axillary hyperhidrosis in patients ≥9 years of age (glycopyrronium cloth, 2.4%, for topical use)[2]
- Pharmacokinetic (PK) and safety data were evaluated in an open-label, phase 1 study of topical GT and oral glycopyrrolate solution
- Population PK analyses were performed using data from two double-blind, phase 2 studies in patients with primary axillary hyperhidrosis across a range of glycopyrronium concentrations from the administration of GT or glycopyrronium bromide (HH01 [NCT02016885], HH02 [NCT02129660])

OBJECTIVES

- To compare the PK, safety, and tolerability of topical GT to orally dosed glycopyrrolate in an open-label, phase 1 study
- To assess the relationship of the topical glycopyrronium PK profile to anticholinergic-related adverse events or efficacy using a population PK and pharmacodynamic model applied to data from two phase 2 studies

METHODS

Study Design

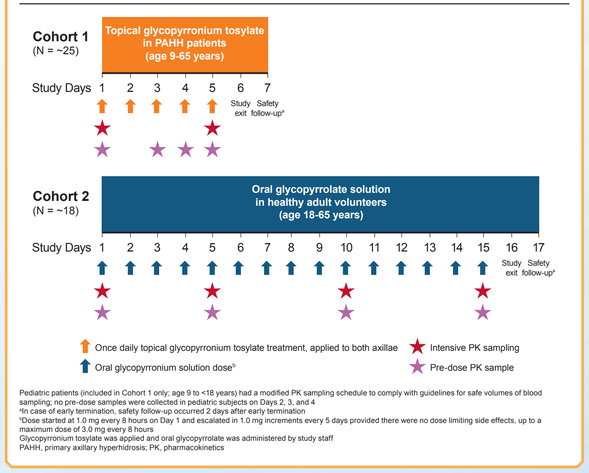
Open-Label Phase 1 Study

- GT 2.4% was applied by study staff (controlling for application method and preventing non-axillary exposure) once daily to both axillae of patients 9 to 65 years of age with primary axillary hyperhidrosis for 5 days (**Figure 1**)
  - Pediatric patients (9 to <18 years) participating in a GT open-label extension study (NCT02553798), were allowed to participate concurrently in this study; these patients underwent a 7-day wash-out of GT prior to Day 1 of this study
  - Patients eligible for the GT arm of the trial had primary axillary hyperhidrosis for ≥6 months, gravimetrically measured sweat production of ≥50 mg/5 min in each axilla, Axillary Sweating Daily Diary (ASDD) Item 2 (severity) score ≥4 (0 to 10 numeric rating scale), and Hyperhidrosis Disease Severity Scale (HDSS) grade 3 or 4
- Oral glycopyrrolate solution was administered to healthy adult volunteers 18 to 65 years of age every 8 hours for 15 days, starting at 1.0 mg and titrated in 1.0 mg increments every 5 days (max 3.0 mg/8 hr), provided there were no dose limiting side effects (**Figure 1**)
- Blood samples were collected on Days 1-5 in patients treated with GT and Days 1, 5, 10, and 15 in those administered with oral glycopyrrolate
  - GT-treated subjects underwent intensive PK sampling on Days 1 and 5 and a pre-dose PK sample on Days 3, 4, and 5; pediatric subjects (9 to <18 years of age) had a modified PK sampling schedule to comply with guidelines regarding safe volumes of blood sampling; no samples were collected in pediatric subjects on Days 2, 3, and 4
  - Oral glycopyrrolate-treated subjects underwent intensive PK sampling on Days 1, 5, 10, and 15
  - Noncompartmental PK analysis was conducted using WinNonlin (version 6.3, Pharsight Corp., Mountain View, CA)
- Adverse events (AEs) were recorded throughout the study
- A safety follow-up telephone call was conducted on Day 7, or 2 days after the subject early-terminated in patients treated with GT, and on Day 17, or 2 days after the subject stopped dosing in subjects treated with oral glycopyrrolate
- The PK evaluable population included subjects who received study drug and had ≥1 PK sample collected
- Concentration values excluded from analysis were any PK samples with
  - Detectable concentrations of glycopyrronium in pre-dose samples on Day 1, and
  - Plasma concentration values ≥3 standard deviations from the mean value for a given time point

Double-Blind Phase 2 Studies (HH01, HH02)

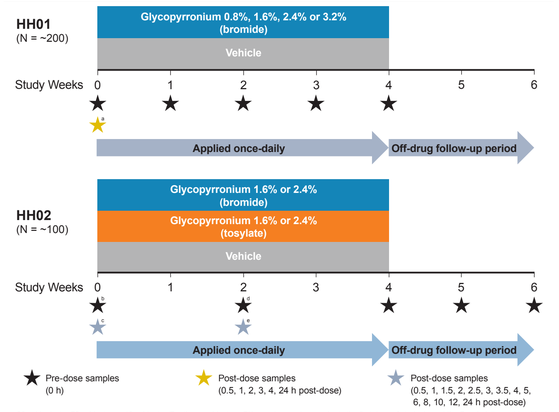
- In HH01, adult patients (>18 years of age) with primary axillary hyperhidrosis were randomized 1:1:1:1:1 to one of 4 doses of topical glycopyrronium bromide (0.8%, 1.6%, 2.4%, 3.2%) or vehicle (**Figure 2**)
- In HH02, adult patients (>18 years of age) with primary axillary hyperhidrosis were randomized 1:1:1:1:1 to one of 2 doses of GT (1.6%, 2.4%), one of 2 doses of glycopyrronium bromide (1.6%, 2.4%), or vehicle (**Figure 2**)
  - Under physiologic conditions, glycopyrronium bromide and GT dissociate, generating the glycopyrronium cation; therefore, the pharmacological activity is mediated by the active moiety, glycopyrronium; glycopyrronium has equivalent binding affinity for the M3 muscarinic acetylcholine receptor in vitro when delivered as either the bromide or the tosylate salt[3]
- Patients were to apply study drug to both axillae once daily for 4 weeks with a 2-week off-drug follow-up
- PK data were collected from a subgroup in each study, and AEs and efficacy data were recorded
- In both studies, intensive blood sampling occurred on Days 1-2 and, for one study also on Days 15-16; additional sampling occurred in subsequent weeks
- PK data from these phase 2 studies informed a population PK model (NONMEM version 7.2.0 Icon PLC, Dublin, Ireland) from which exposure metrics were used to assess the relationship between topical glycopyrronium PK and anticholinergic-related AEs or efficacy

Figure 1. Phase 1 Open-Label Study Design



Pediatric patients (included in Cohort 1 only; age 9 to <18 years) had a modified PK sampling schedule to comply with guidelines for safe volumes of blood sampling; no pre-dose samples were collected in pediatric subjects on Days 2, 3, and 4
[a]In case of early termination, safety follow-up occurred 2 days after early termination
[b]Dose started at 1.0 mg every 8 hours on Day 1 and escalated in 1.0 mg increments every 5 days provided there were no dose limiting side effects, up to a maximum dose of 3.0 mg every 8 hours
Glycopyrronium tosylate was applied and oral glycopyrrolate was administered by study staff
PAHH, primary axillary hyperhidrosis; PK, pharmacokinetics

Figure 2. Phase 2 Double-Blind Study Design



[a]n= 32 subjects; [b]n=79 subjects; [c]n=10 subjects; [d]For these subjects, a PK sample was drawn prior to the first dose of study drug at the Day 1 visit; [e]n =14 subjects
h, hours; PK, pharmacokinetics

Assessments

Open-Label Phase 1 Study

- PK was assessed through collection of blood samples at pre-specified time points for determination of plasma concentrations of glycopyrronium
- The plasma concentrations of glycopyrronium measured in the subjects were used to calculate the following key PK parameters: maximum plasma concentration (C_{max}), area under the plasma concentration versus time curve from 0 to 24 hours ($AUC_{0\text{-}24}$), area under the plasma concentration versus time curve from 0 to 6 hours ($AUC_{0\text{-}6}$), and terminal elimination phase half-life ($T_{1/2}$)
- Safety was assessed through AEs, local skin reactions (GT-treated patients only), safety laboratory tests (serum chemistry, hematology, and urinalysis), vital signs, physical examinations, and electrocardiograms

Population PK Analysis of Double-Blind Phase 2 Studies (HH01, HH02)

- Three databases were assembled
  - Population PK database: all concentration data from the active treatment arms from HH01 and HH02 were pooled into a single NONMEM database
  - Population PK AE database: included information on glycopyrronium exposure and the most severe grade of AEs that could be due to anticholinergic activity
    - Three categories of AEs were defined as
      1. Dry mouth alone
      2. Dry mouth, vision blurred, urinary retention, dry eye, mydriasis, urinary hesitation, urine flow decreased, dry tongue
      3. All events in group 2 plus constipation, nasal dryness, vulvovaginal dryness
    - The worst reported grade was captured using a numerical code (0 for no events, 1 for mild, 2 for moderate and 3 for severe) for all patients (including those randomized to the vehicle arm)
  - Population PK PD database: included information on glycopyrronium exposure and multiple assessments of gravimetric and HDSS scores

RESULTS

Open-Label Phase 1 Study

Subject Disposition and Baseline Characteristics

- In the phase 1 study, 11 adult (mean age 26 years, 63.6% female) and 20 pediatric patients (mean age 14.8 years, 65.0% female) received topical GT, and 18 adults (mean age 44.0 years, 88.9% male) received oral glycopyrrolate (**Table 1**)

Table 1. Phase 1 Open-Label Subject Disposition and Baseline Characteristics

Characteristic	Topical Glycopyrronium Tosylate Adults N=11	Topical Glycopyrronium Tosylate Pediatric (9 to <18 y) N=20	Oral Glycopyrrolate Adults N=18
Subjects			
Enrolled/Completed	11/11	20/20	18/18
Safety Population[a]	11	20	18
PK Evaluable Population[b]	11	20[c]	18
Age			
Mean (SD)	26.0 (8.92)	14.8 (1.64)	44.0 (10.35)
Min, Max	18, 49	10, 17	18, 58
Gender, n (%)			
Male	4 (36.4)	7 (35.0)	16 (88.9)
Female	7 (63.6)	13 (65.0)	2 (11.1)
Race, n (%)			
White	9 (81.8)	13 (65.0)	9 (50.0)
Black or African American	2 (18.2)	7 (35.0)	8 (44.4)
Other	0	0	1 (5.6)
Ethnicity, n (%)			
Hispanic or Latino	2 (18.2)	0	2 (11.1)
Not Hispanic or Latino	9 (81.8)	20 (100.0)	16 (88.9)
Weight (kg), mean (SD)	87.8 (27.7)	67.2 (16.9)	80.2 (9.8)
BMI (kg/m²), mean (SD)	29.4 (6.3)	23.9 (5.6)	27.2 (2.4)

[a]Subjects who were enrolled and received ≥1 confirmed dose of study drug; [b]Subjects who received study drug and had ≥1 PK sample collected; [c]19 and 20 subjects, respectively, were included in PK evaluable population for Day 1 and Day 5
BMI, body mass index; PK, pharmacokinetics; SD, standard deviation

PK Findings

- In adults treated with GT, PK parameters (mean ± SD) were C_{max} 0.08 ± 0.04 ng/mL, $AUC_{0\text{-}6h}$ 0.20 ± 0.14 h*ng/mL, and $AUC_{0\text{-}24}$ 0.88 ± 0.57 h*ng/mL (**Table 2**); similar results were observed for pediatric patients (**Table 3**)
- For adults receiving oral glycopyrrolate 1, 2, and 3 mg, respectively, mean ± SD PK parameters were C_{max} 0.15 ± 0.12, 0.23 ± 0.11, and 0.38 ± 0.19 ng/mL, and $AUC_{0\text{-}24}$ 2.12 ± 1.47, 3.50 ± 1.50, and 5.50 ± 2.19 h*ng/mL ± SD (**Table 2**)

Table 2. PK Findings for Oral Glycopyrrolate vs. Topical Glycopyrronium Tosylate

Oral vs Topical Adults	C_{max} mean ± SD ng/mL	$AUC_{0\text{-}24}$ mean ± SD ng h/mL	$T_{1/2}$ h
Oral Glycopyrrolate[a]			
1 mg/q 8 h (N=18, Day 5/15)	0.154 ± 0.118	2.12 ± 1.47	2.59 ± 0.649[b]
2 mg/q 8 h (N=18, Day 10/15)	0.227 ± 0.106	3.50 ± 1.5	2.8 ± 0.481[c]
3 mg/q 8 h (N=18, Day 15/15)	0.381 ± 0.190	5.50 ± 2.19	2.76 ± 0.879[d]
Topical Glycopyrronium Tosylate[a] (N=11, Day 5/5)	0.08 ± 0.04	0.88 ± 0.57	Could not be determined[e]

[a]Fasting; [b]n=14; [c]n=11; [d]n=12; [e]A clear terminal elimination phase was not evident following topical glycopyrronium tosylate administration due to a lack of concentrations above the lower limit of quantitation; thus, no half-life could be reported in adult and pediatric patients
AUC, area under the plasma concentration over time curve; C_{max}, maximum plasma concentration; h, hours; PK, pharmacokinetics; SD, standard deviation; $T_{1/2}$, elimination (terminal) half life

Table 3. PK Findings for Topical Glycopyrronium Tosylate in Adult vs. Pediatric Patients

Adult vs Pediatric (Topical)	C_{max} mean ± SD ng/mL	$AUC_{0\text{-}24}$ mean ± SD ng h/mL	T_{max} median (range) h
Adult Patients	0.08 ± 0.04 (n=11)	0.88 ± 0.57 (n=7)	1 (0,10) (n=11)
Pediatric Patients	0.07 ± 0.06 (n=20)	Not calculated[a]	1.5 (0,6) (n=19)

[a]Pediatric samples were only collected up to 6 hours post-dose per guidelines on safe blood sampling therefore $AUC_{0\text{-}24}$ could only be determined for adults
AUC, area under the plasma concentration over time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetics; SD, standard deviation; T_{max}, time to maximum plasma concentration

Safety

- No anticholinergic-related treatment-emergent adverse events (TEAEs) occurred with GT, while those occurring with oral glycopyrrolate included dry mouth (16.7%) and nasal dryness (5.6%) (**Table 4**)
- No treatment related TEAEs were reported with GT (**Table 4**)

Table 4. Safety Findings (Topical Glycopyrronium Tosylate versus Oral Glycopyrrolate)

n (%)	Topical Glycopyrronium Tosylate N=31			Oral Glycopyrrolate N=18
	Adult N=11	Pediatric N=20	Total N=31	
TEAEs	**2 (18.2)**	**3 (15.0)**	**5 (16.1)**	**7 (38.9)**
Dry mouth[a]	0	0	0	3 (16.7)
Headache	2 (18.2)	2 (10.0)	4 (12.9)	1 (5.6)
Nocturia	0	0	0	2 (11.1)
Chest Pain	0	0	0	1 (5.6)
Hypoaesthesia	0	0	0	1 (5.6)
Nasal dryness[a]	0	0	0	1 (5.6)
Cough	0	1 (5.0)	1 (3.2)	0
Laceration	0	1 (5.0)	1 (3.2)	0
Rhinorrhea	0	1 (5.0)	1 (3.2)	0
TEAE by severity				
Mild	2 (18.2)	3 (15.0)	5 (16.1)	7 (38.9)
Moderate	0	0	0	0
Severe	0	0	0	0
Treatment-related TEAE	0	0	0	5 (27.8)
Serious TEAEs	0	0	0	0
TEAE leading to discontinuation	0	0	0	0

[a]TEAEs ascribed to anticholinergic effects occurred only with oral glycopyrrolate solution
TEAE, treatment-emergent adverse event

Double-Blind Phase 2 Studies (HH01, HH02)

Subject Demographics and Baseline Characteristics

- In the population PK analysis, 985 PK samples from 108 patients (mean age 32.6 years, 55.6% male) and AE/efficacy data for 137 patients (n=108 glycopyrronium, n=29 vehicle; mean age 32.8 years, 53.3% male) were included (**Table 5**)
- Because of the large number of subjects from both studies that had no measurable glycopyrronium concentrations, a mixture of models approach was used where patients were classified as "absorbers" (eg, those that had measurable glycopyrronium concentrations) and "non-absorbers" (eg, those who never had measurable glycopyrronium concentrations)
  - It is not known what factor(s) may lead to this difference in absorption (eg, drug application variability, skin thickness, etc)

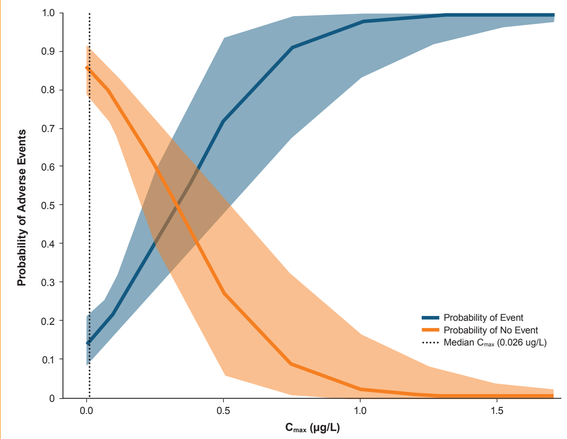
Table 5. Phase 2 Double-Blind Subject Demographics and Baseline Characteristics

Characteristic	PK Database N=108	PK AE & PD Database N=137
Demographics		
Age		
Mean (SD)	32.6 (11.6)	32.8 (11.2)
Min, Max	18, 72	18, 72
Gender, n (%)		
Male	60 (55.6)	73 (53.3)
Female	48 (44.4)	64 (46.7)
Race, n (%)		
Caucasian	94 (87.0)	121 (88.3)
Black	10 (9.3)	12 (8.8)
Asian	1 (0.9)	1 (0.7)
Other	3 (2.8)	3 (2.2)
Weight (kg), mean (SD)	84.1 (22.6)	83.4 (22.2)
BMI (kg/m²), mean (SD)	28.4 (6.2)	28.0 (6.0)
Other Characteristics		
Formulation, n (%)		
Glycopyrronium bromide	66 (61.1)	66 (48.2)
Glycopyrronium tosylate	42 (38.9)	42 (30.6)
Vehicle	NA	29 (21.2)
Status[a], n (%)		
Absorber	71 (65.7)	NA
Non-absorber	37 (34.3)	

[a]Absorbers were those that had measurable glycopyrronium concentrations; non-absorbers were those who never had measurable glycopyrronium concentrations
AE, adverse event; BMI, body mass index; NA, not applicable; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation

- Bioavailability was low (<0.5%)
- There was no evidence of accumulation with repeat dosing
- Systemic exposure did not predict efficacy
- Anticholinergic AEs were associated with higher glycopyrronium concentrations; however, the median C_{max} value was low (0.026 µg/L [min, max (0, 1.67)]; **Figure 3**)

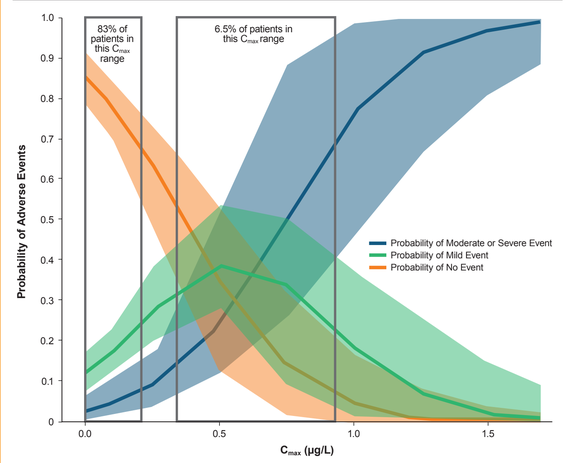
Figure 3. Probability of Anticholinergic Adverse Events (Frequency)



Shading denotes the 95% confidence interval; patients randomized to vehicle were assigned a value of "0" for glycopyrronium exposure
C_{max}, maximum plasma concentration; max, maximum; min, minimum; PK, pharmacokinetics

- A low probability of mild AEs is expected at low peak concentrations (**Figure 4**)
- The probability of moderate/severe AEs does not become appreciable (over 20%) until C_{max} values of approximately 0.2 ug/L; however, most patients did not reach this level (**Figure 4**)
- Most patients (83%) had a relatively low glycopyrronium C_{max} (gray box on the left; **Figure 4**)
- 6.5% of patients had a higher glycopyrronium C_{max} (gray box on the right, **Figure 4**)
- For comparison, pooled AEs of two 4-week, phase 3, double blind studies of GT showed that mild AEs were experienced by 22.8% of vehicle patients and 37.0% GT-treated patients; moderate AEs were experienced by 9.5% of vehicle patients and 18.1% of GT patients, and severe AEs were experienced in 0% of vehicle patients, and 0.9% of GT patients; adverse events infrequently led to discontinuation in those phase 3 studies (<4%)[4]

Figure 4. Probability of Anticholinergic Adverse Events (Severity)



Shading denotes the 95% confidence interval
AE, adverse event; C_{max}, maximum plasma concentration

CONCLUSIONS

- In the phase 1 study, systemic absorption of glycopyrronium was lower in those treated with GT compared with oral glycopyrrolate, consistent with the lack of anticholinergic AEs observed with GT in this study
- Exposure-response models suggest that the probability of AEs increases in frequency and severity with increasing glycopyrronium C_{max}, while efficacy may be mediated locally versus systemically
- PK parameters of GT indicate limited systemic absorption and a low risk of AEs with proper administration
  - Consistent with these PK modeling results from Phase 2 data, most TEAEs in the Phase 3 double-blind trials were mild

REFERENCES

1. Doolittle et al. *Arch Dermatol Res*. 2016;308(10);743-9.
2. QBREXZA™ (glycopyrronium) cloth [Prescribing Information]. Dermira, Inc., Menlo Park, CA. 2018.
3. Glycopyrronium Muscarinic M3 Receptor Binding, Life Technologies Corporation, 13-24.
4. Glaser et al. *J Am Acad Dermatol*. 2019 Jan;80(1):128-138.e2.

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AUTHOR DISCLOSURES

DMP: Paid consultant and investigator for Dermira, Inc. **ELL, RM, DRM:** Paid consultant for Dermira, Inc. **JD:** Employee of Dermira, Inc.

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