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. It affects 4-6% of the United States (US) population, or approximately 13.5 million people1

• Glycopyrronium tosylate (GT) is a topical anticholinergic approved in the US for treatment of primary axillary hyperhidrosis in patients 18 years of age or older2

• Pharmacokinetic (PK) and safety data were evaluated in an open-label, phase 1 study of topical GT and oral glycopyrrolate tosylate3

• 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 0.5% to 2.4%4

OBJECTIVES

• To compare the PK, safety, and tolerability of topical GT to orally dosed glycopyrronium 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 to study staff (controlling for application method and preventing non-salivary exclusion) once daily to both axillae of patients 9 to 65 years of age with primary axillary hyperhidrosis for 14 days (Figure 1, Study Days 1-2)

• Patients were randomized to one of 3 treatment groups: GT 0.5%, GT 1.6%, or GT 2.4%

• Blood samples were collected on Days 1 and 2, Days 1-5 in patients treated with GT, and Days 1, 5, 10, and 15 in patients treated with oral glycopyrrolate

• Oral glycopyrrolate was 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 of 16 mg daily

• For comparison, pooled AE data of two 4-week, phase 3, double-blind studies of GT showed that mild anticholinergic AEs were associated with higher glycopyrronium concentrations; however, the median Cmax value was low (0.008 µg/mL, min 0.00005, max 0.0103) Figure 2

• 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 Cmax value was low (0.008 µg/mL, min 0.00005, max 0.0103) Figure 2

RESULTS

• Plasma concentration values ≥3 standard deviations from the mean value for a given time point

• Detectable concentrations of glycopyrronium in pre-dose samples on Day 1, and

• Plasma concentrations x3 standard deviations from the means value for a given time point

Double-Blind Phase 2 Studies (HH01, HH02)

• In HH01, adult patients (18-65 years of age) with primary axillary hyperhidrosis were randomized 1:1:1 to one of 4 doses of topical glycopyrronium bromide (0.5%, 1.6%, 2.4%, or 3.2% or vehicle) (Figure 2, Study Days 1-15)

• In HH02, adult patients (18-65 years of age) with primary axillary hyperhidrosis were randomized 1:1:1:1 to one of 2 doses of GT (1.6%, 2.4%), or 2 doses of 0.5% glycopyrronium bromide (0.5%, 2.4%) or vehicle (Figure 2)

• Under physiological conditions, glycopyrronium bromide and GT coexist, generating the glycopyrronium cation; therefore, the pharmacological activity is mediated by the muscarinic acetylcholine receptor and not when delivered either the bromide or the tosylate salt

• Patients were to apply study drug to both axillae once daily for 4 weeks with a 2-week off-drug follow-up

• PK data from these two phase 2 studies is now a population PK model (NONMEM version 7.2.0 licensed PL, Dublin, Ireland) from which exposure metrics were used to assess the relationship between topical glycopyrronium PK and anticholinergic-related AEs or efficacy

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed/Enrolled</td>
<td>20/20</td>
</tr>
<tr>
<td>Evaluable Population</td>
<td>11/11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Males, Females</td>
<td>10, 11</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>60 (60%)</td>
</tr>
<tr>
<td>Race (%)</td>
<td>Black or African American 32 (32%), White 68 (68%)</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td>Hispanic or Latin American 10 (10%), Other 90 (90%)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>76.8 (16.1)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>25.9 (5.5)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glaspyrronium 0.5%</th>
<th>Glaspyrronium 1.6%</th>
<th>Glaspyrronium 2.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.008 ± 0.004</td>
<td>0.008 ± 0.004</td>
<td>0.008 ± 0.004</td>
</tr>
<tr>
<td>AUC∞ (µg·h/mL)</td>
<td>0.005 ± 0.002</td>
<td>0.005 ± 0.002</td>
<td>0.005 ± 0.002</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pediatric Patients</th>
<th>Adult Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.008 ± 0.004</td>
<td>0.008 ± 0.04</td>
</tr>
<tr>
<td>AUC∞ (µg·h/mL)</td>
<td>0.005 ± 0.002</td>
<td>0.005 ± 0.002</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oral Glycopyrrolate</th>
<th>Topical Glycopyrronium Tosylates</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs (%)</td>
<td>2.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Nasal drynessa</td>
<td>0.227 ± 0.106</td>
<td>0.127 ± 0.057</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0.227 ± 0.106</td>
<td>0.127 ± 0.057</td>
</tr>
<tr>
<td>Headache</td>
<td>0.227 ± 0.106</td>
<td>0.127 ± 0.057</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.227 ± 0.106</td>
<td>0.127 ± 0.057</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.227 ± 0.106</td>
<td>0.127 ± 0.057</td>
</tr>
<tr>
<td>Dry eye</td>
<td>0.227 ± 0.106</td>
<td>0.127 ± 0.057</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>0.227 ± 0.106</td>
<td>0.127 ± 0.057</td>
</tr>
<tr>
<td>Urinary hesitation</td>
<td>0.227 ± 0.106</td>
<td>0.127 ± 0.057</td>
</tr>
<tr>
<td>Urine flow</td>
<td>0.227 ± 0.106</td>
<td>0.127 ± 0.057</td>
</tr>
<tr>
<td>Overall AE rate</td>
<td>19.0%</td>
<td>12.7%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HH01</th>
<th>HH02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD) 59.8 (13.5)</td>
<td>Mean (SD) 44.0 (10.3)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>Female 16 (88.9%)</td>
<td>Female 13 (65.0%)</td>
</tr>
<tr>
<td>Race (%)</td>
<td>Black or African American 1 (5.6%)</td>
<td>Black or African American 2 (10.5%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean (SD) 77.7 (15.9)</td>
<td>Mean (SD) 73.3 (15.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean (SD) 28.9 (5.2)</td>
<td>Mean (SD) 27.0 (5.5)</td>
</tr>
</tbody>
</table>

Figure 2. Phase 2 Double-Blind Study Design

Figure 3. Probability of Anticholinergic Adverse Events (Frequency)

Figure 4. Probability of Anticholinergic Adverse Events (Severity)