Challenges and Solutions associated with Dermal Dosing and Plasma Analysis in the Clinic for a repurposed compound

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Acknowledgements

AMS- Accelerator Mass Spectrometry

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Stiefel, a GSK company, US

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Overview

• Disease Background
• Study Design
• Analytical Results
• Summary and Conclusions
Disease Background
Hyperhidrosis

- Hyperhidrosis Definition: excessive sweating beyond what is physiologically required to maintain normal thermal regulation of the body.

- Can affect the axilla, palms, soles of the feet, face, and other areas. Hyperhidrosis can have a debilitating effect on the quality of life for the individual. In the US it affects 3% of the population.\(^1\)

\(^1\): Strutton et al, (2004)
Background

Compound

- Umeclidinium (UMEC) is potent pan-active Long-Acting Muscarinic Antagonist (LAMA)
- Inhaled UMEC is an approved therapy for COPD
- Currently UMEC is under investigation for Hyperhidrosis

- **Sweat gland control**
  - 5 subtypes of muscarinic receptors identified in different locations of human eccrine glands
  - Acetylcholine release stimulates postsynaptic muscarinic receptors in eccrine glands

- **Mechanism of action/Therapeutic rationale**
  - UMEC acts as an inhibitor to these muscarinic receptors
  - Another LAMA (glycopyrrolate) appears to be effective as a topical therapy in hyperhidrosis\(^2\)
  - To date, no topical therapies have achieved regulatory approval

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**COPD – Chronic Obstructive Pulmonary Disease**

2: Hays, (1978)
Background

Skin Structure

Epidermis:
(Stratum Corneum, Variable thickness)

Dermis: Sweat receptors

Subcutaneous tissue
Study Design

Background

- **Primary Objective**: To characterise the PK profile of UMEC in humans after a single topical administration to axilla or palm in healthy male subjects

- Evidence from respiratory data shows that UMEC has absorption-limited PK

- Necessary to characterise the terminal elimination phase of PK

- **Secondary Objective**: To investigate the safety

- Study is based on applying dose to the axilla/palm with combinations of occlusion/non-occlusion

- Occlusion can increase absorption by up to 10 fold \(^3\)

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3: Zhai H (2001)
Rationale for using $[^{14}\text{C}]-$labeling

- Systemic concentrations following dermal administration predicted to be low and non-quantifiable by traditional Mass Spectrometry methods
- $[^{14}\text{C}]-$labeling in combination with AMS gives a highly sensitive assay
- LC+AMS method (LLQ=348 fg/mL) Validated Sep 2013, at GSK, Ware, UK

Dosimetry
- Extensive work was carried out prior to the study to ensure that the effective radioactive dose was $<1$ mSv. (Category IIa, ICRP guidelines)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Radioactivity (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual exposure of average UK resident in 1 year</td>
<td>2.3</td>
</tr>
<tr>
<td>1 abdominal x-ray</td>
<td>1</td>
</tr>
<tr>
<td>Return flight across the</td>
<td>0.07</td>
</tr>
<tr>
<td>1 chest x-ray</td>
<td>0.05</td>
</tr>
</tbody>
</table>

ICRP-International Commission on Radiological Commission
Study Design

Design:
- Open-label, single dose;
- Planned up to 4 sequential cohorts:
  - Axillary unoccluded/occluded
  - Palmar unoccluded/occluded
  - 6 subjects/ cohort
- Single dose of 165 mg (~ 666 kBq/18 μCi) of a 1.85% (w/w) solution of $^{14}$C]UMEC applied over a 40 cm$^2$ surface area
  (actual UMEC dose of 3 mg, effective whole body dose of 0.2 mSv)
- Feasibility assessment and stopping criteria after each cohort
Procedures:

• For the axilla, hair clipped ~ 12hr before dosing

• The dose was applied via Pipette, blood sampling 0 to 72 hr

• After 8 hr the dose was washed off

• Washings were counted by LSC on site results reported within 24 hrs (would not be as quick with a non-radioactive dose)

• AMS results for plasma total radioactivity were reported within 2 weeks

• AMS parent PK data was reported within the following 4 weeks
Feasibility Assessment
Systemic Concentration Prediction

![Graph showing systemic concentration prediction over time after product application, with key markers for different concentrations and time points.](image-url)
AMS Analysis

LC + AMS method summary

- 1 mL of human plasma* was extracted by protein precipitation
- The extract dried down and reconstituted in 250 µL
- 100 µl was injected onto HPLC system (25 min. runtime to separate metabolites)
- Parent fraction collected at approx 14 min.
- Fraction dried, then graphitised and taken for AMS analysis
- LLQ = 348 fg/mL, HLQ 94.2 pg/mL
- 1 week procedure

*The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents”

Following the Analysis of the washings, on site LSC Results showed that approx. 81% of the dose was recovered from the skin surface.
Analytical Results
Cohort B- Occluded Axilla

Following the Analysis of the washings, on site LSC Results showed that approx. 74% of the dose was recovered from the skin surface.
Analytical Results
Cohort D- Occluded Palm

• Following the on site analysis of the washings, X% recovered

• Data showed that not all of the dose was recovered from the skin

All data NQ (<348 fg/mL)

• Thickness of palm stratum corneum ~ 170 µm vs other areas ~ 20 µm

• This does not necessarily equate to lack of activity (effect site is dermis)
## Study QC Summary Data for LC+AMS Assay

### Summary of Statistical Parameters

<table>
<thead>
<tr>
<th>Summary of Statistical Parameters</th>
<th>Quality Control Sample Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.18 pg/mL</td>
</tr>
<tr>
<td>Overall Mean</td>
<td>1.22</td>
</tr>
<tr>
<td>Standard Deviation (within run means)</td>
<td>0.19</td>
</tr>
<tr>
<td>Precision (%)</td>
<td>15.6</td>
</tr>
<tr>
<td>Bias (%)</td>
<td>3.2</td>
</tr>
<tr>
<td>n</td>
<td>18</td>
</tr>
</tbody>
</table>

Statistics calculated from rounded data
Conclusions and Summary

- Study has provided indirect evidence that UMEC penetrates to the site of action
- Study has enabled generation of a PopPK model for dermally applied UMEC
- Variability in Stratum Corneum thickness can greatly affect absorption
- Occlusion (axilla) increased systemic exposure by 3.8 fold
- Sensitive bioanalytical assay was required
- \(^{14}\text{C}\) Labelling allowed fast turnaround at site and highly sensitive assay (LC+AMS, 348 fg/mL LOQ)
- Key learning's around dermal dosing Axilla vs Palm were gained
- This study was a bridging study for Ph2a Proof Of Concept study
- Study has set a ‘template’ for future dermal studies
References


Thank you

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