Assessment of the Human Systemic Absorption of Sunscreen Active Ingredients: FDA-Sponsored Randomized Clinical Trial

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Disclaimer

This presentation reflects the views of the speaker and should not be construed to represent FDA’s views or policies.
Overview

• Background
• Primary Objective
• Study Design
• Outcomes
• Results
• Conclusions
• Coming Next
Background

- Sunscreens prevent sunburn - reflect or absorb ultraviolet radiation
- Sunscreen products applied in substantial amounts multiple times every day over course of lifetime
- Active ingredients are organic chemicals, some have been shown to be absorbed through human skin with detectable levels in the blood or urine
- Little known about the systemic exposures, understanding the systemic exposure and its clinical relevance is important
- FDA guidance “Nonprescription Sunscreen Drug Products Safety and Effectiveness Data” requests the assessment of the human systemic absorption of sunscreen ingredients with a Maximal Usage Trial (MUsT).
- This study is not intended to meet all requirements of MUsT studies, but will follow many of the principles to assess maximal use of a single sunscreen formulation
Primary Objective

• To explore whether the active components of 4 sunscreen products are absorbed into the systemic circulation when a sunscreen product is applied under maximal-use conditions
  • Avobenzone
  • Oxybenzone
  • Octocrylene
  • Ecamsule
Tested Products

- Spray
  - Avobenzone 3%
  - Oxybenzone 6%
  - Octocrylene 2.35%
  - Homosalate 15%
  - Octisalate 5%

- Spray
  - Avobenzone 3%
  - Oxybenzone 5%
  - Octocrylene 10%

- Lotion
  - Avobenzone 3%
  - Oxybenzone 4%
  - Octocrylene 6%

- Cream
  - Avobenzone 3%
  - Octocrylene 10%
  - Ecamsule 2%
Study Design

- Subjects: Healthy Volunteers; 18 – 60 years
- Open-label, randomized 4 group parallel study

- Dose: 2 mg/cm²
  75% of body

- Duration: Every two hours, 4 doses/day; 4 days

- PK sample: 30 samples
  pre-dose to 144 h
  (intensive on days 1 & 4)
Outcomes

• **Primary Outcome:**
  • Maximum plasma concentration (Cmax: day 1 to 7) of Avobenzone

• **Secondary Outcome:**
  • Maximum plasma concentration of Oxybenzone, Octocrylene and Ecamsule

• **Exploratory Outcomes:**
  • $C_{\text{max}}$ on day 1 and 4
  • Time at which Cmax occurs on day 1, 4 and overall
  • AUC on day 1, 4 and overall
  • Residual concentrations on each day
  • Half-life of each ingredient

• **Post-hoc Assessments:**
  • Number and percentage of participants with plasma concentration exceeding 0.5 ng/mL on day 1
  • Drug accumulation from day 1 to 4
Statistical Analysis

- 24 participants were randomized to receive 1 of the 4 treatments
- Randomization was conducted in block sizes of 4
- Not blinded due to differences in formulation types
- Data was reported with standard descriptive statistics
- Accumulation with repeat dosing was assessed by log-transforming AUC and maximum plasma concentration from day 1 and 4 for each ingredient
# Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Study (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (Mean ± SD)</td>
<td>35.5 ± 10.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>14 (58.3 %)</td>
</tr>
<tr>
<td>White</td>
<td>9 (37.5 %)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Body mass index, kg/m² (Mean ± SD)</td>
<td>25.0 ± 2.9</td>
</tr>
<tr>
<td>Body surface area, m² (Mean ± SD)</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Fitzpatrick skin type</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Type 2</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Type 3</td>
<td>5 (20.8%)</td>
</tr>
<tr>
<td>Type 4</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Type 5</td>
<td>8 (33.3%)</td>
</tr>
<tr>
<td>Type 6</td>
<td>6 (25.0%)</td>
</tr>
</tbody>
</table>
Systemic Exposure of Avobenzone

Matta et al., JAMA 2019;321(21):2082-2091
Systemic Exposure on Day 1

Spray#1: 8h – 100%
Spray#2: 8h – 83%
Lotion: 8 h – 100%
Cream: 8h – 83%

Matta et al., JAMA 2019;321(21):2082-2091
Systemic Exposure of Oxybenzone

Matta et al., JAMA 2019;321(21):2082-2091
Systemic Exposure on Day 1

100% of subjects had levels above 0.5ng/mL in 2hrs

Matta et al., JAMA 2019;321(21):2082-2091
Systemic Exposure of Octocrylene

Matta et al., JAMA 2019;321(21):2082-2091
Systemic Exposure on Day 1

100% of subjects in 6h
Except Spray#1

Matta et al., JAMA 2019;321(21):2082-2091
5 of 6 participants has $C_{\text{max}}$ more than 0.5 ng/mL on day 1

Matta et al., JAMA 2019;321(21):2082-2091
$C_{\text{max}}$ on Day 1 versus Day 4

![Chart showing concentration (ng/ml) for Avobenzone, Oxybenzone, and Octocrylene on Day 1 and Day 4. The chart indicates a higher concentration on Day 4 for each compound.](chart.png)
Residual Concentrations

The diagram shows the residual concentrations of different analytes over time. The analytes include Avobenzone, Oxybenzone, and Octocrylene. The concentrations are measured in ng/ml and are represented at different time points (95, 120, 144). The data points indicate the variability in concentration over time for each analyte.
Conclusions

• All active ingredients in all tested products exhibited systemic exposures above the threshold for potentially waiving some nonclinical toxicology studies for sunscreens

• The systemic exposures supports the need for further studies to determine the clinical significance

• These results do not indicate that individuals should refrain from the use of sunscreen
Coming Next

• A second clinical study was performed to characterize:
  – Systemic exposure of additional active ingredients
  – Systemic exposure after a single application
  – Time to clear from body
Study Design of Second Clinical Trial

- Subjects: Healthy Volunteers; 18 – 60 years; More subjects
- Open-label, randomized 4 group parallel study

Dose: 2 mg/cm²
75% of body

Single Application on Day 1
Four applications per day from day 2 to 4

PK samples: 30 samples pre-dose to 480 h
(intensive on days 1 & 4)

Skin sample: Tape stripping (Day 7 and 14)
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Preliminary Communication

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Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

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Filling in the Evidence About Sunscreen

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