FDA Sunscreen Absorption Study Part 2

Murali K. Matta, PhD

Division of Applied Regulatory Science
Office of Clinical Pharmacology
U.S. Food and Drug Administration
Disclaimer

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

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

Murali K. Matta, PhD
Overview

• Recap - Study 1
• Study Design Study 2
• Outcomes
• Summary
Recap: Study 1 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)
Recap: Findings from Study 1

- Systemic exposure data of most commonly used ingredients under maximal usage conditions
- 6 subjects were adequate to detect systemic exposure of these sunscreen active ingredients
- All the tested active ingredients in all tested products reached systemic exposures above 0.5 ng/mL
  - All active ingredients reached above 0.5 ng/mL on day 1
- All tested ingredients have long terminal half-lives
  - Skin could be serving as a depot
Unknowns

- Systemic exposure after a single application
- Systemic exposures of additional active ingredients
Unknows

• Systemic exposure after a single application
• Systemic exposures of additional active ingredients

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

Murali K. Matta, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Jeffry Florian, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

Tested Products

- Lotion: Avobenzone 3% Oxybenzone 4% Octocrylene 6%
- Aerosol Spray: Avobenzone 3% Oxybenzone 6% Octocrylene 10% Homosalate 15% Octisalate 5%
- Non Aerosol Spray: Avobenzone 3% Homosalate 10% Octinoxate 7.5% Octisalate 5% Octocrylene 10%
- Pump Spray: Avobenzone 3% Homosalate 10% Octinoxate 7.5% Octisalate 5% Octocrylene 6%
Tested Products

Part 1

Lotion
Avobenzone 3%
Oxybenzone 4%
Octocrylene 6%

Aerosol Spray
Avobenzone 3%
Oxybenzone 6%
Octocrylene 10%
Homosalate 15%
Octisalate 5%

Non Aerosol Spray
Avobenzone 3%
Homosalate 10%
Octinoxate 7.5%
Octisalate 5%
Octocrylene 10%

Pump Spray
Avobenzone 3%
Homosalate 10%
Octinoxate 7.5%
Octisalate 5%
Study Design

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

Dose: 2 mg/cm²
75% of body
Study Design

• Subjects: Healthy Volunteers; 18 – 60 years;
• 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
Study Design

- Subjects: Healthy Volunteers; 18 – 60 years;
- 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 sample: Pre-dose to 480 h
intensive sampling on days 1 & 4
Study Design

- Subjects: Healthy Volunteers; 18 – 60 years;
- 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 sample: **Pre-dose to 480 h**
  Intensive sampling on days 1 & 4
- Skin sampling: **Tape stripping**
  (Day 7 and 14)
Outcomes

• **Primary Outcome:**
  • Maximum plasma concentration of Avobenzone
Outcomes

• **Primary Outcome:**
  • Maximum plasma concentration of Avobenzone

• **Secondary Outcome:**
  • Maximum plasma concentration of other active ingredients
Outcomes

- **Primary Outcome:**
  - Maximum plasma concentration of Avobenzone

- **Secondary Outcome:**
  - Maximum plasma concentration of other active ingredients

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

- Data was reported with standard descriptive statistics
## Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Population Total (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (Mean ± SD)</strong></td>
<td>38.7 ± 13.2</td>
</tr>
<tr>
<td><strong>Female sex N (%)</strong></td>
<td>24 (50%)</td>
</tr>
<tr>
<td><strong>Race N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>23 (48 %)</td>
</tr>
<tr>
<td>White</td>
<td>23 (48 %)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Ethnicity N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>45 (94%)</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m² (Mean ± SD)</strong></td>
<td>26.0 ± 2.9</td>
</tr>
<tr>
<td><strong>Body surface area, m² (Mean ± SD)</strong></td>
<td>1.9 ± 0.2</td>
</tr>
</tbody>
</table>
## Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Population Total (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (Mean ± SD)</td>
<td>38.7 ± 13.2</td>
</tr>
<tr>
<td>Female sex N (%)</td>
<td>24 (50%)</td>
</tr>
<tr>
<td>Race N (%)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>23 (48 %)</td>
</tr>
<tr>
<td>White</td>
<td>23 (48 %)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Ethnicity N (%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>45 (94%)</td>
</tr>
<tr>
<td>Body mass index, kg/m2 (Mean ± SD)</td>
<td>26.0 ± 2.9</td>
</tr>
<tr>
<td>Body surface area, m² (Mean ± SD)</td>
<td>1.9 ± 0.2</td>
</tr>
</tbody>
</table>
Systemic Exposure of Avobenzone

![Graph showing systemic exposure of Avobenzone over time for different forms of application: Lotion, Nonaerosol Spray, Aerosol Spray, and Pump Spray. The graph illustrates concentration (ng/mL) over time (hr) with Day 1 indicated.](image)
Systemic Exposure of Avobenzone

Graphs showing concentration levels over time for different forms of Avobenzone application: Lotion, Nonaerosol Spray, Aerosol Spray, and Pump Spray. The graphs illustrate concentration levels in ng/mL over 480 hours, with peaks and troughs indicating variability in exposure levels.
Systemic Exposure of Oxybenzone
Systemic Exposure of Octocrylene

Day 1

Concentration (ng/mL)

Time (hr)

Concentration (ng/mL)

Time (hr)

- Lotion
- Nonaerosol Spray
- Aerosol Spray
Systemic Exposure of Homosalate

Day 1

Concentration (ng/mL)

Time (hr)

Concentration (ng/mL)

Time (hr)

Nonaerosol Spray
Aerosol Spray
Pump Spray
Systemic Exposure of Octisalate

Day 1

Concentration (ng/mL) vs Time (hr)

- Nonaerosol Spray
- Aerosol Spray
- Pump Spray
Systemic Exposure of Octinoxate

Day 1

Concentration (ng/mL)

Time (hr)

Nonaerosol Spray

Pump Spray

Concentration (ng/mL)

Time (hr)
### C\textsubscript{max} on Day 1 versus Day 4

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Day 1</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avobenzene</td>
<td>1.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Oxybenzone</td>
<td>94.2</td>
<td>252</td>
</tr>
<tr>
<td>Octocrylene</td>
<td>1.5</td>
<td>6.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Day 1</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homosalate</td>
<td>3.8</td>
<td>12.5</td>
</tr>
<tr>
<td>Octisalate</td>
<td>0.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Octinoxate</td>
<td>1.1</td>
<td>5.3</td>
</tr>
</tbody>
</table>
$C_{\text{max}}$ on Day 1 versus Day 4
\( C_{\text{max}} \) on Day 1 versus Day 4
Exposures of 1 vs 4 applications of Lotion

![Graph showing concentration over time for Avobenzone, Oxybenzone, and Octocrylene in Study Part 1 and Part 2.](image-url)
Skin Amounts

Lotion

- Avobenzone
- Oxybenzone
- Octocrylene

Pump Spray

- Homosalate
- Octisalate
- Octinoxate

Active ingredient in skin (ng/cm²)

- D7
- D14
Skin Amounts

![Graph showing the amount of active ingredients in skin for Avobenzone, Oxybenzone, Octocrylene, Homosalate, Octisalate, and Octinoxate in Lotion and Pump Spray forms at Days 7 and 14.](image-url)
Skin Amounts

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Lotion</th>
<th>Pump Spray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avobenzone</td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
</tr>
<tr>
<td>Oxybenzone</td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
</tr>
<tr>
<td>Octocrylene</td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
</tr>
<tr>
<td>Homosalate</td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
</tr>
<tr>
<td>Octisalate</td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
</tr>
<tr>
<td>Octinoxate</td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
<td><img src="D7" alt="Graph" /> <img src="D14" alt="Graph" /></td>
</tr>
</tbody>
</table>
Summary

- FDA conducted 2 different trials to demonstrate the feasibility of these studies and collect preliminary data of 7 different sunscreen active ingredients.
Summary

• FDA conducted 2 different trials to demonstrate the feasibility of these studies and collect preliminary data of 7 different sunscreen active ingredients

• Current study was performed with a modified design in 48 healthy volunteers (24 men and 24 women) randomly assigned to receive 1 of 4 formulations (lotion or 1 of 3 sprays)
Summary

• FDA conducted 2 different trials to demonstrate the feasibility of these studies and collect preliminary data of 7 different sunscreen active ingredients

• Current study was performed with a modified design in 48 healthy volunteers (24 men and 24 women) randomly assigned to receive 1 of 4 formulations (lotion or 1 of 3 sprays)

• Instead of studying only maximal-use conditions, on the first day, only 1 application of sunscreen was performed
Summary

- FDA conducted 2 different trials to demonstrate the feasibility of these studies and collect preliminary data of 7 different sunscreen active ingredients.
- Current study was performed with a modified design in 48 healthy volunteers (24 men and 24 women) randomly assigned to receive 1 of 4 formulations (lotion or 1 of 3 sprays).
- Instead of studying only maximal-use conditions, on the first day, only 1 application of sunscreen was performed.
- All the 6 active ingredients studied (avobenzone, oxybenzone, octocrylene, homosalate, octisalate, and octinoxate) were absorbed, and this absorption occurred on the first day after a single application (applied to 75% of the body surface area).
Summary

• FDA conducted 2 different trials to demonstrate the feasibility of these studies and collect preliminary data of 7 different sunscreen active ingredients

• Current study was performed with a modified design in 48 healthy volunteers (24 men and 24 women) randomly assigned to receive 1 of 4 formulations (lotion or 1 of 3 sprays)

• Instead of studying only maximal-use conditions, on the first day, only 1 application of sunscreen was performed

• All the 6 active ingredients studied (avobenzone, oxybenzone, octocrylene, homosalate, octisalate, and octinoxate) were absorbed, and this absorption occurred on the first day after a single application (applied to 75% of the body surface area)

• The active ingredients remained in plasma for extended time periods after the last application (3, 6, or 17 days, depending on the active ingredient), even in skin
Summary

• FDA conducted 2 different trials to demonstrate the feasibility of these studies and collect preliminary data of 7 different sunscreen active ingredients

• Current study was performed with a modified design in 48 healthy volunteers (24 men and 24 women) randomly assigned to receive 1 of 4 formulations (lotion or 1 of 3 sprays)

• Instead of studying only maximal-use conditions, on the first day, only 1 application of sunscreen was performed

• All the 6 active ingredients studied (avobenzone, oxybenzone, octocrylene, homosalate, octisalate, and octinoxate) were absorbed, and this absorption occurred on the first day after a single application (applied to 75% of the body surface area)

• The active ingredients remained in plasma for extended time periods after the last application (3, 6, or 17 days, depending on the active ingredient), even in skin

• The fact that the sunscreen active ingredients are absorbed systemically does not mean they are unsafe. Rather, this finding calls for further testing to determine the safety of those ingredients for repeated use over a lifetime
# Acknowledgements

<table>
<thead>
<tr>
<th><strong>DARS/OCP</strong></th>
<th><strong>DNDP/OND</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>David Strauss</td>
<td>Steven Adah</td>
</tr>
<tr>
<td>Jeffry Florian</td>
<td>Sergio Coelho</td>
</tr>
<tr>
<td>Robbert Zusterzeel</td>
<td>Jian Wang</td>
</tr>
<tr>
<td>Vikram Patel</td>
<td>Lesley-Anne Furlong</td>
</tr>
<tr>
<td>Nageswara Pilli</td>
<td>Charles Ganley</td>
</tr>
<tr>
<td>Donna Volpe</td>
<td>Theresa Michele</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>DCPIII/OCP</strong></th>
<th><strong>DPQR/OTR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Luke Oh</td>
<td>Yang Yang</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>OCP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dennis Bashaw</td>
</tr>
<tr>
<td>Issam Zineh</td>
</tr>
</tbody>
</table>
Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

Murali K. Matta, PhD; Jeffry Florian, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Yang Yang, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

Murali K. Matta, PhD; Jeffry Florian, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Yang Yang, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

Additional Slides....
Consort Diagram Study 2

91 Healthy volunteers assessed for eligibility

36 Not randomized
   36 Excluded (not eligible)
      22 Did not meet inclusion criteria
      6 Declined to participate
      8 Out of screening window
      7 Eligible to be replacement participant

48 Participants randomized

12 Randomized to receive lotion
   12 Received lotion as randomized

12 Randomized to receive spray #3
   12 Received spray #3 as randomized

12 Randomized to receive spray #4
   12 Received spray #4 as randomized

12 Randomized to receive spray #5
   12 Received spray #5 as randomized

0 Lost to follow-up
   0 Discontinued intervention

0 Lost to follow-up
   0 Discontinued intervention

0 Lost to follow-up
   2 Discontinued intervention
   2 Withdrew (adverse event [rash])

0 Lost to follow-up
   2 Discontinued intervention
   2 Withdrew (adverse event [rash])

12 Included in analysis

12 Included in analysis

12 Included in analysis

12 Included in analysis

12 Included in analysis