PQRI Workshop

Present Experience and Challenges with the Use of Pharmacodynamics Evaluation of BE of Glucocorticoids – Industry Perspective

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and
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Evaluation of BE of Topical Glucocorticoids

- Vasoconstrictor assay by McKenzie and Stoughton to assess potency (1962, Visual assessment of blanching)
- Prior to July 1, 1992, BE based on single-time point, 8 to 16 hour exposure, Stoughton-McKenzie method
- July 1992, FDA issued interim guidance modified M-S:
  - N = 36 healthy subjects
  - Dose: Volume (5-40 mcl), dose = duration (0.25 – 6 & 16 hrs.)
  - Generic & RLD applied to separate arms
  - Minolta ChromaMeter and visual evaluations over 24 hours
  - Washout and repeat, reversing arms for generic & RLD
  - $E_{\text{max}}$ models fit to each subject’s response (AUEC)
Evaluation of BE of Topical Glucocorticoids

• Between 1992-1994, industry attempted unsuccessfully to use the interim guidance.
  - Failures due to high within-site variability (80+ %)
  - NAPM & GPA Topical Task Force
  - FDA Internal and External Expert Panels

• 2 June 1995, FDA issued a new Guidance for Topical Dermatologic Corticosteroids: In Vivo Bioequivalence
Evaluation of BE of Topical Glucocorticoids

1995 Draft Guidance

Separate Dose-Response Pilot in 12 Screened Responders

- Response = vasoconstriction (Area Under the Effect Curve over 24 hours)
- \( E_{\text{max}} \) Model:
  \[
  E = \frac{E_{\text{max}} \cdot \text{Dose}}{ED_{50} + \text{Dose}}
  \]
  \[
  E = \frac{E_{\text{max}} \cdot \text{Dose}^\gamma}{ED_{50} + \text{Dose}^\gamma}
  \]
- \( E_{\text{max}} \) is Maximal Response
- Dose of Half-Maximal Response (\( ED_{50} \))
- \( \gamma \) = Hill Coefficient
Evaluation of BE of Topical Glucocorticoids

1995 Draft Guidance

Pivotal Study in Pre-screened Responders to get 40-60 Detectors

- $D_1 = \text{Dose for } 1/3 E_{\text{max}} \text{ Response (Reference Product)}$
- $D_2 = \text{Dose for } 2/3 E_{\text{max}} \text{ Response (Reference Product)}$
- Generic and Reference BE evaluation at $ED_{50}$ duration
- Response = vasoconstriction (AUEC)
- Qualified Detectors demonstrate response of $D_2/D_1 \geq 1.25$
- 90% Confidence Interval for Test/Reference AUEC Ratio
Simple and Sigmoid $E_{\text{max}}$ Models with D1, ED$_{50}$ & D2
Evaluation of BE of Topical Glucocorticoids

Minolta Chroma Meter
Evaluation of BE of Topical Glucocorticoids

Minolta Chroma Meter

L*a*b* color space and color difference $\Delta E_{ab}$

COLOR SPACE

White

A

A'

$\Delta E_{ab}$

L*

Yellow

Green

Red

Blue

Gray

level as specimen's color
Evaluation of BE of Topical Glucocorticoids

$E_{\text{max}}$ Modeling

• Population Fit of Dose-Response Data
  ➢ Non-Mem
  ➢ P-Pharm (first used by FDA)
  ➢ Kinetica
  ➢ SAS Proc Nlin Mixed
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$E_{\text{max}}$ Modeling

Initial Estimate

Final Estimate
Evaluation of BE of Topical Glucocorticoids

$E_{\text{max}}$ Modeling

Initial Estimate

Final Estimate
Evaluation of BE of Topical Glucocorticoids

$E_{\text{max}}$ Modeling
## Evaluation of BE of Topical Glucocorticoids

### $E_{\text{max}}$ Modeling

<table>
<thead>
<tr>
<th>Initial Estimates</th>
<th>P-Pharm Final Estimates</th>
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<tbody>
<tr>
<td><strong>ED50</strong></td>
<td><strong>Emax</strong></td>
</tr>
<tr>
<td>60</td>
<td>-10</td>
</tr>
<tr>
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Evaluation of BE of Topical Glucocorticoids

Some Challenges with Dose Response Pilot

- DR evaluation needed before DR pilot study
- Impractically short ED$_{50}$
- Low $E_{\text{max}}$ (low AUEC for many doses)
- Truncation of Vasoconstrictor Response
- Bi-phasic dose response
**DR Evaluation Needed Before DR Pilot Study**

Dose = 0.25, 0.5, 1, 1.5, 2, 4, and 6 hrs

<table>
<thead>
<tr>
<th>Class</th>
<th>Product</th>
<th>ED50 (min)</th>
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<tbody>
<tr>
<td>1</td>
<td>Clobex Lotion, 0.05%</td>
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<tr>
<td>1</td>
<td>Vanos Cream, 0.1%</td>
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<tr>
<td>2</td>
<td>Topicort Cream, 0.25%</td>
<td>30</td>
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<tr>
<td>4</td>
<td>Elocon Cream, 0.1%</td>
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<tr>
<td>5</td>
<td>DesOwen Lotion, 0.05%</td>
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<tr>
<td>6</td>
<td>Aclovate Cream, 0.05%</td>
<td>85</td>
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<tr>
<td>6</td>
<td>Aclovate Ointment, 0.05%</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>Aclovate Ointment, 0.05%**</td>
<td>110</td>
</tr>
</tbody>
</table>

**Occluded**
Impractically Short ED$_{50}$

$E_{\text{max}}$ Model: ED50 = 0.5, $E_{\text{max}}$ = -45

Mean (N = 20)
Low $E_{max}$

Adjusted A-Scale Readings vs. Time

Mean Reading

Reading Time in Hours

- Baseline
- AUEC = -5
- AUEC = -8
- AUEC = -14
- AUEC = -20
Low $E_{\text{max}}$
Truncation of Vasoconstrictor Response

Mean Adjusted a-Scale Reading vs. Hour After Removal
Bi-Phasic Dose Response
Evaluation of BE of Topical Glucocorticoids

Other Challenges

- Having to include all subjects in the dose ranging study but removing non-detector subjects from the Pivotal study
- Determining the appropriate sample size for the Pivotal study (VAR of mean ≠ σ²/n)
Evaluation of BE of Topical Glucocorticoids

Key References

Interim Guidance, Topical Corticosteroids: *in vivo* bioequivalence and *in vitro* release methods. Division of Bioequivalence and Division of Anti-infective Drug Products, CDER, FDA, 1 July 1992

Guidance for Industry, Topical Dermatologic Corticosteroids: *in vivo* bioequivalence, CDER, FDA, 2 June 1995