Human Dermal Safety Testing for Topical Drug Products

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John Lyssikatos
Senior Director, Business Development
Speakers

Derek Grimes
Vice President, Clinical Research

Derek joined TKL in 2007; bringing 19+ years of research related management experience. He directs TKL’s core business and clinical site operational functions, P&L, clinical/project management, site management, recruitment services. He provides expertise on protocol designs and recruitment strategies. Prior to TKL Research, Derek spent 8 years with Columbia University and NYU. He holds a Bachelor of Science in Health Administration from St Joseph’s College (NY).

John Lyssikatos
Senior Director, Business Development

John joined TKL Research in 2012, bringing over 29 years of CRO experience, focused in dermatology. He manages and supports client relationships in the pharmaceutical, health and personal care industries. He provides experience in consulting, designing and executing full service clinical programs. Prior to joining TKL, John was with Hill Top Research for 23 years, where he held a broad range of leadership positions, including operations, technical and business development. Mr. Lyssikatos holds a B.S. degree in Chemistry from Rutgers University.
The views and opinions expressed in the following PowerPoint slides are those of the individual presenters and should not be attributed to TKL Research’s or the FDA’s policy and views.

These PowerPoint slides are the intellectual property of the individual presenters and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved.
Derek Grimes presentation focus:
- The what, when and why of Dermal Safety Studies
- The overall study designs for these programs
- The different patch types in Dermal Safety programs
- The evaluation process

John Lyssikatos presentation focus:
- The different scoring scales for Dermal Safety Studies
- The data analysis approach
- What are the operational considerations
- The sponsor consultation
Why Conduct Dermal Safety Testing

- Risk Assessment of Investigational Drug
  - Assist with topical drug development program
  - Assessing tolerance under exaggerated conditions
- Regulatory Requirements
  - Phase I Profile
    - Irritation Potential
    - Sensitization Potential
    - Photo Irritation/Sensitization Potential
When to Conduct Dermal Safety Testing

- Following Pre-Clinical and early Phase I (PK)
  - Recommend Irritation Study
    - Assess highest concentration potential

- In Parallel or upon completion of Phase III
Requested Studies

- Cumulative Irritation Patch Test (CIPT)
- Contact Sensitization (Human Repeat Insult Patch Test –HRIPT)
- Phototoxicity
- Photoallergy

Notes:
- Performed under exaggerated conditions to elicit specific response
- Single center studies
- Combination studies (CIPT/HRIPT)
- Waiver may be granted for photobiology studies
- May be required for various routes of administration (i.e. transdermal, oral)
Cumulative Irritation Patch Test (CIPT)

Clinical Centers: 1
Duration: 21 days
Visits: 22
Patch Application: 24 hours
Patch Conditions: Fully Occluded
Evaluations: Daily (24 hrs. post application)
Subjects: 30 Healthy Normal
Test Articles: Active, Vehicle, Controls (Positive & Negative), Reference (optional)

Notes:
• 14 Day Model
• Abraded Skin
Clinical Studies

Contact Sensitization
Human Repeat Insult Patch Test
Jordan King Design

Clinical Centers: 1
Duration: 6 weeks (3 week Induction, 2 week rest period, 1 week challenge)
Visits: 15
Patch Applications: 9 Induction and 1 Challenge for 48/72 hours
Patch Conditions: Fully or Semi-Occluded
Evaluations: Induction (48 to 72 hrs.) Challenge (1, 24, 48 and 72 hrs)
Subjects: 200 Healthy Normal
Test Articles: Active, Vehicle, Controls (optional) Reference (optional)
Re-Challenge: As needed (minimum 4 weeks following Challenge)
Phototoxicity

Evaluating photo-irritation potential under solar simulated conditions

Clinical Centers: 1
Duration: 4 days
Visits: 4
Patch Application: Double set (non and irradiated), single 24 hour application
Patch Conditions: Fully or Semi-Occluded
Evaluations: Daily (24 hrs. post application, 24 and 48 hours post irradiation)
Subjects: 30 Healthy Normal, Fitzpatrick Skin Types I, II, III
Test Articles: Active, Vehicle, Non-Irradiated Control
UV Light: UVA and UVB (290-400 nm) exposure
Photoallergy
Evaluating photo-allergic potential under solar simulated conditions

Clinical Centers: 1
Duration: 6 weeks (3 week Induction, 2 week rest period, 1 week challenge)
Visits: 17
Patch Application: Double set (non and irradiated), 6 Induction and 1 Challenge for 24 hours
Patch Conditions: Fully or Semi-Occluded
Evaluations: Daily (24 hrs. post application, 24 and 48 hours post irradiation) and daily during challenge
Subjects: 50 Healthy Normal, Fitzpatrick Skin Types I, II, III
Test Articles: Active, Vehicle, Non-Irradiated Control
UV Light: UVA and UVB (290-400 nm) exposure
Re-Challenge: As needed (minimum 4 weeks following Challenge)
Clinical Studies

Solar Light Company
Evaluation Process

Patches

TKL Patch System  Finn Chambers  Hill Top Chamber

Application

• By Volume or Weight
• 0.2 mL or 0.2 gm
• Eppendorf Research® Pipette, Syringes, Spatulas
Skin Graders

- Principal Investigator (PI), Sub-PI or Trained Graders
- Trained by our Dermatologist (bi-annual)
- PI reviews all dermal reactions
- PI provides conclusions for Clinical Study Report (CSR)
Evaluation Process

Standard Grading Techniques

• Minimize intra-graders (maintain primary and one secondary grader)

• Viewing the Skin - “adequate light source to illuminate the application sites”

• Evaluate each site separately

• Before touching, obtain general evaluation of the skin site

• Palpate skin if necessary when checking for edema/papular response
Pathophysiology of Skin Reactions

- Tissue injury
- Inflammatory process begins
- Varies with intensity/extent of tissue damage
- Signs of inflammation
  - Erythema
  - Edema
  - Papules, vesicles, bullae
  - Heat, pain, itching, etc.
Common Dermatological Terms used to Describe Skin Irritation/Sensitization

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>A form of macule, diffused redness. A patch of redness of the skin</td>
</tr>
<tr>
<td>Macule</td>
<td>Discolored spot or patch of the skin</td>
</tr>
<tr>
<td>Edema</td>
<td>Skin tissues contain excessive amounts of fluid</td>
</tr>
<tr>
<td>Induration</td>
<td>Hardened skin tissue</td>
</tr>
<tr>
<td>Papule</td>
<td>Elevated area, solid and circumscribed, generally red</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Localized collection of fluid, small blister-like elevations</td>
</tr>
<tr>
<td>Bulla</td>
<td>Large blister or vesicle</td>
</tr>
</tbody>
</table>
Evaluation Process

Examples

- Erythema
- Edema
- Papules
- Vesicles
- Bulla
- Induration
Berger/Bowman Scoring Scale

Response Symbols and Numerical Equivalents

<table>
<thead>
<tr>
<th>Grade</th>
<th>Score*</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>No evidence of irritation</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Minimal erythema; barely perceptible</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Definite erythema, readily visible; or minimal edema; or minimal papular response</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Erythema and papules</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Definite edema</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>Erythema, edema, and papules</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>Vesicular eruption</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>Strong reaction spreading beyond test site</td>
</tr>
</tbody>
</table>

Notes:
- Validated Scales
- Scale is designed to describe irritation
- It is not linear, i.e. score of 4 is not twice as bad as a 2
Berger/Bowman Scoring Scale

Effects on Superficial Layers of Skin

<table>
<thead>
<tr>
<th>Grade</th>
<th>Score*</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>Slight glazed appearance</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>Marked glazing</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>Glazing with peeling and cracking</td>
</tr>
<tr>
<td>F</td>
<td>3</td>
<td>Glazing with fissures</td>
</tr>
<tr>
<td>G</td>
<td>3</td>
<td>Film of dried serous exudate covering all or portion of the patch site</td>
</tr>
<tr>
<td>H</td>
<td>3</td>
<td>Small petechial erosions and/or scabs</td>
</tr>
</tbody>
</table>
Scoring Scales

Application of Scoring Scale

The grading from the erythema and superficial layers of the skin are taken into consideration when scoring an irritation response.

- We will combine the score from the numeric and letter grades to determine the overall score
- A score of 3 or higher will be analyzed as a grade 3 score
- The score will be carried throughout the remaining evaluation days
- The patch site will no longer be patched

Examples:

2 (Definite erythema, readily visible; or minimal edema; or minimal papular response)
B (Glazing with peeling and cracking)

Scoring 2+2 = 4 Reported as a 3

Residual scores (evaluations of patch sites with no additional applications) are evaluated until the reaction subsides. We see this in the HRIPT studies.
# Scoring Scales

## Other Notations

<table>
<thead>
<tr>
<th>Notation</th>
<th>Response/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Spreading of reaction beyond patch study site (ie, reaction where study material was not in contact with the skin).</td>
</tr>
<tr>
<td>B</td>
<td>Burning or stinging sensation</td>
</tr>
<tr>
<td>p</td>
<td>Papular response &gt;50%</td>
</tr>
<tr>
<td>pv</td>
<td>Papulovesicular response &gt;50%</td>
</tr>
<tr>
<td>D</td>
<td>Damage to epidermis: oozing, crusting and/or superficial erosions</td>
</tr>
<tr>
<td>I</td>
<td>Itching</td>
</tr>
<tr>
<td>X</td>
<td>Subject absent</td>
</tr>
<tr>
<td>PD</td>
<td>Patch dislodged</td>
</tr>
<tr>
<td>NA</td>
<td>Not applied</td>
</tr>
<tr>
<td>NP</td>
<td>Not patched (due to reaction achieved)</td>
</tr>
<tr>
<td>N9G</td>
<td>No ninth grading</td>
</tr>
<tr>
<td>NSS</td>
<td>New Naïve Site under Semi-Occlusive patch conditions due reactions achieved at original patch site</td>
</tr>
<tr>
<td>NSOP</td>
<td>New Naïve Site under Open patch conditions due to reactions achieved at original patch site</td>
</tr>
<tr>
<td>T</td>
<td>Tape related reaction</td>
</tr>
</tbody>
</table>
## Scoring Scales

### Similar Grading Scales

<table>
<thead>
<tr>
<th>Response</th>
<th>Symbol</th>
<th>Numerical Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythema</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reaction</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Mild, but definite erythema</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>Moderate erythema</td>
<td>++</td>
<td>2</td>
</tr>
<tr>
<td>Marked/severe erythema</td>
<td>+++</td>
<td>3</td>
</tr>
<tr>
<td><strong>Edema</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reaction</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Mild, but definite edema</td>
<td>**</td>
<td>1</td>
</tr>
<tr>
<td>Definite edema with erosion/vesiculation</td>
<td>***</td>
<td>2</td>
</tr>
</tbody>
</table>
### Scoring Scales

#### Similar Grading Scales

<table>
<thead>
<tr>
<th>Response/Comment</th>
<th>Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperpigmentation</td>
<td>Hr</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>Ho</td>
</tr>
<tr>
<td>Vesiculation</td>
<td>V</td>
</tr>
<tr>
<td>Papular response</td>
<td>p</td>
</tr>
<tr>
<td>Papulovesicular response</td>
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<td>Damage to epidermis: oozing, crusting, and/or superficial erosions</td>
<td>D</td>
</tr>
<tr>
<td>Itching</td>
<td>I</td>
</tr>
<tr>
<td>Spreading of reaction beyond patch study site (ie, reaction where material did not contact skin)</td>
<td>S</td>
</tr>
<tr>
<td>Follicular irritation with or without pustule formation (folliculitis)</td>
<td>f</td>
</tr>
<tr>
<td>Subject absent</td>
<td>X</td>
</tr>
<tr>
<td>Patch dislodged</td>
<td>PD</td>
</tr>
<tr>
<td>Not patched</td>
<td>NP</td>
</tr>
<tr>
<td>No reaction</td>
<td>0</td>
</tr>
</tbody>
</table>
The sample size of 30 evaluable subjects conforms to industry and regulatory standards for determination of dermal cumulative irritation potential.

The primary variable of interest is the mean cumulative irritation score. The total cumulative irritation score for each subject and product will also be calculated as the sum of irritation scores.

These parameters will be tested pairwise for product differences using Fisher’s protected least significant differences in the context of the 2-way analysis of variance (ANOVA), including main effects of subject and product, without interaction. Pairwise differences will be tested only if the null hypothesis of a common mean score for all products is rejected at the 5% level.

Once the maximum score of a 3 or greater is achieved, the cumulative irritancy score will be calculated as the maximum score of 3 for that individual site for the remainder of the study.
The sample size of 200 evaluable subjects conforms to industry and regulatory standards for determination of dermal sensitization potential. In the absence of any sensitization reactions, a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

Cumulative Irritancy
Cumulative irritancy during Induction will be quantified by means of the cumulative irritancy index (CII), defined as the mean of the total cumulative irritation scores received during the Induction Phase (9 readings). The CII will be tested pairwise for product differences using Fisher’s protected least significant differences in the context of the 2-way analysis of variance (ANOVA) including main effects of subject and product, without interaction. Pairwise differences will be tested for all products at the 5% level.

Analysis of Dermal Sensitization Potential
A narrative description of reactions in the Challenge and Re-Challenge Phases will be provided together with the opinion of the Investigator as to whether such reactions are felt to be indicative of contact sensitization.
Phototoxicity
The sample size of 30 evaluable subjects conforms to industry and regulatory standards for determination of irritation when topical application to skin is followed by light exposure.

Local Tolerability Assessment
Selected pairwise comparisons will be performed on the mean of the Day 3 and Day 4 response scores (sum of erythema and edema scores) in the context of the analyses of variance (ANOVA). Pairs to be compared are: each study product irradiated versus non-irradiated and all pairwise comparisons of each set (study product name versus study product vehicle on both the irradiated and non-irradiated sites and study product name versus untreated and study product vehicle versus untreated on the irradiated sites).
**Photoallergy**
The sample size of 50 evaluable subjects conforms to industry and regulatory standards for determination of irritation/sensitization when topical application to skin is followed by light exposure.

**Assessment of Responses**
The mean score by subject and treatment, including all scores assigned during Induction, will be analyzed using Fisher’s least significant differences in the analysis of variance (ANOVA) with factors subject and treatment. All pairwise comparisons will be performed: Product Name on both the irradiated and non-irradiated sites, and Vehicle on both the irradiated and non-irradiated sites.

**Photosensitivity**
The determination of dermal photosensitization potential will be made by the Investigator based on specific scoring criteria derived from observations in the Challenge Phase of the study and confirmed in the Re-Challenge Phase, if necessary.
Operational Considerations

Phase I vs. Phase III

- Single Center
- Recruitment Strategy
- Pre-Screening Procedures
  - Safety labs not always required
  - Increases recruitment, timelines and cost
- Block Enrollment of Subjects
- Compressed Timelines
  - Database
  - Monitoring
- Scheduling
  - Holidays
  - Summer Activities
Consultation

Study Design

• Understanding the Investigational Drug
  • Pre-Clinical data
  • Literature
  • Comparators
  • Known sensitizers and irritants

• Establish Conditions for Success
  • Subject requirements
  • Application process
  • Evaluation process
Study Design

- Incremental Phases
  - Pilot Study to assess preliminary irritation
  - Contingency plan with in protocol
    - Patch conditions, duration, etc.
  - Serial vs parallel execution of multiple programs

Consultation
Consultation

Regulatory

• Communication with regulatory agencies
  • Secure requirements and understanding

• Understanding requirements
  • NCE vs. 505b2 vs. ANDA
  • Following specific guidance

• Management of data
  • Database structure
  • Analysis
  • Reporting (e-CTD)
Thank You