

Human Dermal Safety Testing for Topical Drug Products

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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.

Disclaimer

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Summary

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

Dermal Safety Testing: Objectives

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

Dermal Safety Testing: Objectives

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

Clinical Studies

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)

Clinical Studies

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)

Clinical Studies

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

Clinical Studies

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

Evaluation Process

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

Evaluation Process

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.

Evaluation Process

Common Dermatological Terms used to Describe Skin Irritation/Sensitization

Erythema	A form of macule, diffused redness. A patch of redness of the skin
Macule	Discolored spot or patch of the skin
Edema	Skin tissues contain excessive amounts of fluid
Induration	Hardened skin tissue
Papule	Elevated area, solid and circumscribed, generally red
Vesicle	Localized collection of fluid, small blister-like elevations
Bulla	Large blister or vesicle

Evaluation Process

Examples



Erythema



Edema



Papules



Vesicles



Bulla



Induration

Scoring Scales

Berger/Bowman Scoring Scale

Berger, R.S. and Bowman, J.P. (1982) A reappraisal of the 21-day cumulative irritation test in man. *J. Toxicol.Cut. and Ocular Toxicol.*, 1, 109-115.

Response Symbols and Numerical Equivalents

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

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

Scoring Scales

Berger/Bowman Scoring Scale

Berger, R.S. and Bowman, J.P. (1982) A reappraisal of the 21-day cumulative irritation test in man. *J. Toxicol.Cut. and Ocular Toxicol.*, 1, 109-115.

Effects on Superficial Layers of Skin

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

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

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

Scoring Scales

Similar Grading Scales

Response	Symbol	Numerical Equivalent Score
Erythema		
No reaction	-	0
Mild, but definite erythema	+	1
Moderate erythema	++	2
Marked/severe erythema	+++	3
Edema		
No reaction	-	0
Mild, but definite edema	**	1
Definite edema with erosion/vesiculation	***	2

Scoring Scales

Similar Grading Scales

Response/Comment	Notation
Hyperpigmentation	Hr
Hypopigmentation	Ho
Vesiculation	V
Papular response	p
Papulovesicular response	pv
Damage to epidermis: oozing, crusting, and/or superficial erosions	D
Itching	I
Spreading of reaction beyond patch study site (ie, reaction where material did not contact skin)	S
Follicular irritation with or without pustule formation (folliculitis)	f
Subject absent	X
Patch dislodged	PD
Not patched	NP
No reaction	0

Data Analysis

CIPT

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.

Data Analysis

HRIPT

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.

Data Analysis

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).

Data Analysis

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

Consultation

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

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)

A large, abstract graphic on the left side of the slide, consisting of multiple overlapping, wavy lines in various colors including purple, blue, yellow, and orange. The lines create a sense of motion and depth, resembling a stylized wave or a ribbon.

Thank You

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