

Dermal Safety Studies in Development: Sponsor`s Perspective

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Dermal Safety Studies:

- Cumulative Irritation
- Sensitization
- Phototoxic Potential
- Photosensitization

Content of Presentation

- Timing of Dermal Safety Studies in Drug Development
- Design of Dermal Safety Studies
- Sponsor`s Perspective on Design
- Contribution to Risk Evaluation in Development
- Conclusions

Dermal Safety Studies: 3 Complementary Steps

- Pre-clinical tolerability testing not entirely predictive of human tolerability.
- Tolerability testing in HVs not entirely predictive of tolerability in patients.
- Tolerability testing in patients considered most predictive.
- Note: The three steps are considered complementary to assess & determine dermal safety.

Dermal Safety Studies: Evaluation of Cutaneous Safety of Topical Medications

- In HVs, dermal safety studies might be conducted in Phase 1 (concept formulations) to support formulation optimization & selection.
- In HVs, dermal safety studies are conducted in parallel to Phase 2 or 3 (final-to-be –marketed formulation) to complement evidence of safety generated in patients.
- In Patients, main evidence for dermal safety is generated with final-to-be-marketed formulation, in target population, under intended use conditions in Phase 2 and 3.

Cumulative Irritation: Main Design Elements

- Single Center, randomized, vehicle, negative (petrolatum) and positive controlled (0.25% SLS), evaluator-blinded, intra-individual design
- 30 to 40 HVs
- 3 week study: Test product under occlusion, applied Monday through Friday, left in place over the weekend
- Skin Reaction Assessment on 5 point scale (0 (none) to 4 (severe))

Sensitization: Main Design Elements

- Single center, randomized, vehicle and negative (petrolatum) controlled, evaluator blinded, intra-individual study in HVs.
- 200 evaluable HVs
- Induction: 3 weeks, occlusive patches: 3 Days (M, W, F) /week
- Rest: 2 weeks
- Challenge: 24 hours occlusive patch
- Re-challenge: HVs with equivocal or positive reaction
- Skin Reaction Assessment (5 Point Scale)
- Sensitization Reaction Evaluation (negative, equivocal, positive).

Phototoxic Potential: Main Design Elements

- Single center, randomized, vehicle controlled, evaluator-blinded, intra-individual comparison study in HVs
- 30 evaluable HVs.
- Single dose under occlusion, two sets (irradiated and non-irradiated) test sites on back
- Evaluation: 30min, 24H, 48H
- Skin Reaction (5 point scale: 0 (no reaction) to 4 (erythema with vesicles or erosion or bullae)
- Phototoxic response (0=neg., 1=equivocal, 2=positive)

Photosensitization Potential: Main Design Elements

- Single Center, randomized, vehicle & negative (petrolatum) controlled, evaluator blinded, intra-individual comparison study in HVs
- 50 HVs
- Product: 2 sites under occlusion(with & without irradiation)
- Induction: 3 weeks (3days/w, weekend patches left in place)
- Rest: 2 weeks
- Challenge: 24H patch, after patch removal skin reaction and sensitization reaction assessment.
- Re-challenge: Subjects equivocal or positive sensitization

Dermal Safety Studies: Sponsor`s Perspective on Design

- Pro: Intra-individual, controlled, maximized, testing of multiple concentrations and controls in HVs.
- Con: Testing in HVs might not fully reflect actual tolerability observed in –e.g. atopic (“skin-barrier defect”) -patients.
- Consideration: Intra-individual, controlled studies in patients – e.g. intra-individual (e.g. right-left comparison or small plaque assay) studies – to supplement dermal safety testing in HVs.

Dermal Safety Studies: Perspective Irritation and Sensitization: How Many Studies: One vs. Two?

- In the sensitization study, irritation is assessed during 3 weeks induction and sensitization is assessed during challenge, after two weeks rest.
- Note: The two phases of the study are separated in time by the rest-phase; then, assessments for irritation and sensitization are considered separate and independent.
- Consider: Induction (to study irritation) and challenge phase (to study sensitization) of the sensitization study (200 HVs), will probably suffice, there might be no need to do an additional irritation study (40HVs).

Dermal Safety Studies: Sponsor`s Perspective on Design

- Consider Scales: judgement vs. morphological descriptor scales for assessment of sensitization.
- Consider Scores: individual highest vs. average scores.
- Consider Patch Conditions (occlusion, semi-occlusion) vs . intended actual clinical use: application of test product under maximized conditions might lead to exaggerated irritation and higher sensitization rates.

Dermal Safety Studies: Contribution to Risk Evaluation in Development: Irritation

- HV differ from patients, e.g. patients with skin barrier defect (e.g. atopic dermatitis) are prone to experience higher and /or more severe irritation rate.
- Maximized occlusive conditions might exaggerate irritation potential in HVs compared to the product applied under intended use conditions (e.g. BPO is highly irritating under occlusion, but has acceptable tolerability when applied to treat acne vulgaris).
- Phase 3 studies conducted under intended use conditions generate the decisive evidence - for (known or suspected) irritating products, signs & symptoms of cutaneous tolerability can be evaluated at each study visit using well defined morphological scales (e.g. for erythema, scaling, dryness, stinging/burning); then, study of irritation in HVs is complementary.

Dermal Safety Studies: Contribution to Risk Evaluation in Development: Sensitization

- Frequently, Phase 3 protocols record sensitization as AESIs, sensitization is confirmed by patch-test, including patch test of the formulation components.
- Sensitization study conducted under experimental, maximized conditions in HVs is complementary to Phase 3 in patients using the medication as intended.
- Maximized conditions (occlusion) might increase sensitization rate compared to intended use conditions.

Dermal Safety Studies: Contribution to Risk Evaluation in Development: Phototoxicity & Photosensitization

- For products absorbing light in the terrestrial spectrum, assessment of phototoxicity and photosensitization is required.
- Evaluation of phototoxic potential and photosensitization under controlled & maximized conditions in HVs is helpful to understand risk for “photo-events” under intended use.
- Negative phototoxic potential and photosensitization studies are considered helpful to understand tolerability risk, but need to be confirmed by Phase 3 under intended use in the target population.

Conclusions

- Dermal Safety Studies are part of the dermal safety assessment embedded in the three step complementary evaluation of tolerability.
- Most informative to Patients & Prescribers is Irritation and Sensitization rate under in-use in Phase 2&3 studies (specific assessments of irritation and sensitization are possible).
- Sensitization and irritation studies conducted under maximized conditions in HVs are supportive, but pivotal studies are considered decisive in evaluation of dermal safety of the product.
- Reassuring to Patients & Prescribers: Phototoxic and Photosensitization studies in HVs are reassuring of dermal safety. Pivotal studies are confirmatory.