The Göttingen Minipig in Drug Development for Dermal Products

Dr. med. vet. Sandra Johanssen, ERT

Agenda

- **Introduction:**
  - Specific Issues for Dermal Product Development
  - Minipigs in Dermal Product Development
- Dermal Repeat Dose Toxicity Study in Minipigs
- Dermal Local Tolerance Study in Minipigs
- Summary and Conclusions
Specific Issues for Dermal Products

Specific Matters for Dermal Products – local and systemic exposure

➢ Local toxicity
  - Skin irritation and other effects
  - Skin sensitization
  - Phototoxicity
Specific Issues for Dermal Products

Specific Matters for Dermal Products – local and systemic exposure

- Local toxicity
  - Skin irritation and other effects
  - Skin sensitization
  - Phototoxicity

- Systemic toxicity
  - Target organs
  - Dose dependence
  - Relationship to exposure
  - Reversibility of effects
  - Systemic NOAEL
GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS M3(R2)

5. REPEATED-DOSE TOXICITY STUDIES
The recommended duration of the repeated-dose toxicity studies is usually related to the duration, therapeutic indication and scope of the proposed clinical trial. In principle, the duration of the animal toxicity studies conducted in two mammalian species (one non-rodent) should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the repeated-dose toxicity studies (Table 1). Limit doses/exposures that are considered appropriate in repeated-dose toxicity studies are described in Section 1.5.
Specific Issues for Dermal Products

- Characterization of full toxicity profile needs high systemic exposure → MTD or multiple of human systemic exposure
- Increase dose in topical dermal studies limited (concentration of formulation, application area, amount formulation applied)

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>$\text{AUC}_{0-24\text{h}}$ ng*\text{h/mL} end of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 week mini-pig, dermal</td>
<td>1 g ointment/kg/day (highest feasible conc.)</td>
<td>2.94 (≈ 8x)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.3 (≈ 300x)</td>
</tr>
<tr>
<td>4 week mini-pig, oral</td>
<td>5 mg/kg/day (NOAEL)</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>30 mg/kg/day</td>
<td>871</td>
</tr>
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Possible way for topical dermal products:
Non-rodent (minipig): topical dermal
Rodent: systemic route (s.c., i.v., oral)
Minipigs in Dermal Product Development

Minipig species of choice

- Similarities between minipig and human skin
  - Sparse hair coat
  - Thickness of epidermis:
    - 70-140 mm in minipigs, 50-120 in humans, 10-20 mm in rats

- Differences
  - Man: eccrine sweat gland in major part of body surface area
  - Minipig: apocrine glands (not for thermoregulation)
  - pH on skin surface: man 5, minipig 6-7
Dermal repeat dose toxicity study

Dermal Application of Formulation

- Final clinical formulation
- Vehicle (formulation without drug substance)
- Low dose = clinical strength
- Mid dose
- High dose = increased concentration of active
  - maximum feasible concentration without changing formulation composition

- Maximum feasible dose volume
  - depends on formulation properties

Aqueous gel – cream - ointment
Dermal repeat dose toxicity study

Maximum feasible treatment area

- Back and sites ≈ 10% of body surface area
Dermal repeat dose toxicity study

Maximum feasible treatment area

- Back and sites ≈ 10% of body surface area

Daily treatment time and regimen should mimic clinical use

Consider: protection of application site or open application

- Protection (semi-occlusion): several layers of cotton gauze fixed
  - Prevents spreading of formulation in pens

Pro
- Prevents cross-contamination
- In most cases protection is not in line with clinical application (mostly open)

Con
- Daily application time is limited
- Open application: the formulation can stay on the skin until the next treatment
Dermal repeat dose toxicity study

Systemic exposure with semi occluded (6 h) and open application (24h)

<table>
<thead>
<tr>
<th>Steady state</th>
<th>Open</th>
<th>Semi occl. 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ointment</td>
<td>Ointment</td>
</tr>
<tr>
<td></td>
<td>0.75 g/kg/day</td>
<td>1 g/kg/day</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>AUC0-24h (ng*h/mL)</td>
<td>19</td>
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Dermal repeat dose toxicity study

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Day 1 (open)

![Concentration vs Time Graphs](image-url)
Dermal repeat dose toxicity study

Vehicle control group and untreated control group (shear control)

- The formulation without the active might have an effect on the skin
- 5 groups

- Endpoints
  - Standard endpoint for repeat-dose toxicity study
Dermal repeat dose toxicity study

Vehicle control group and untreated control group (shear control)
• The formulation without the active might have an effect on the skin
• 5 groups

• Endpoints
  • Standard endpoint for repeat-dose toxicity study

Routine repeat dose study but special considerations:
• Minipig species of choice
• Final formulation (vehicle, three different concentrations)
• Two control groups (shear control, vehicle control)
• Maximum feasible dose volume and treatment site
• Daily treatment time and regimen should mimic clinical use
Local Tolerance

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 1 March 2001
CPMP/SWP/2145/00

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON NON-CLINICAL LOCAL TOLERANCE TESTING OF MEDICINAL PRODUCTS
Local Tolerance

1 25 April 2014
2 EMA/CHMP/SWP/2145/2000 Rev.1
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on non-clinical local tolerance testing of medicinal products
5 Draft
A Comparison of Rabbit and Human Skin Response to Certain Irritants

Llewellyn Phillips, II, Marshall Steinberg, Howard I. Maibach, and William A. Akers

Dermatology Research Division, Letterman Army Institute of Research, Presidio of San Francisco, California 94129

Received May 13, 1971

The Draize rabbit test accurately predicted the severe human skin irritants and nonirritants, but failed to separate the mild and moderate skin irritants. Several chemicals considered unsafe by the rabbit test proved nonirritating to human skin. When the rabbit testing was inconclusive, only human testing could separate mild and moderate irritants.

Minipig?
# Local Tolerance

## Difference of erythema gradings in rabbits and minipigs with vehicle formulations

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<tr>
<th>Erythema End of study</th>
<th>Grade</th>
<th>Rabbit 28 day Local tolerance</th>
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</tr>
<tr>
<td>None</td>
<td>0</td>
<td>3/4</td>
<td></td>
</tr>
<tr>
<td>Very slight</td>
<td>1</td>
<td>1/4</td>
<td>2/4</td>
</tr>
<tr>
<td>Well defined</td>
<td>2</td>
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* scabbing and desquamation in 4/4 animals
### Local Tolerance

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* scabbing and desquamation in 4/4 animals

- Difference in reactions more pronounced in scabbing and desquamation than in erythema
Local tolerance

Local tolerance study in minipigs

- 3 application sites per site – 6 application sites per animal
- 6 animals/group
- Application site 4 x 4 cm
Local tolerance study in minipigs

- Semi occlusive (permeable to air), 24 hour treatment time
- 4 weeks, daily application
Local Tolerance

Local tolerance study in minipigs

- 200 mg formulation/application site

- Draize score of erythema and edema plus recording of other dermal findings

- Histopathology of naive skin and application sites
Local Tolerance

Difference of erythema gradings in rabbits and minipigs with vehicle formulations

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Local Tolerance

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* fissures and desquamation in 4/4 animals

- Local tolerance testing with small application areas in minipigs is feasible
- Enables irritation potential-testing of different formulations
Summary and Conclusion

- Minipig is the standard non-rodent species for repeat-dose toxicity studies with dermal application.
- Treatment regimen in dermal repeat-dose toxicity studies is very specific and depends on the formulation and the way of clinical use.
- Local tolerance testing with small application areas is possible in minipigs:
  - Enables testing of several formulations in parallel.
  - Has a better prediction with regard to irritation than rabbits.
Thank you!

Oliver Lüdtke-Handjery
Rainer Lewin
Thomas Lummert
Rainer Ernst