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Trifarotene Cream (AKLIEF®): Formulation screening from *in vitro* Permeation Testing to Clinical studies

Nathalie Wagner

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Agenda

- Context
  - Why formulation screening was needed?
- Selection tool kit
  - *In vitro* skin permeation studies (IVPT)
  - Clinical phase 1 PK study in healthy volunteers
  - Clinical proof of efficacy studies in subject with acne
- Conclusion

Trifarotene: Selection of the To-Be-Marketed formulation

New Chemical Entity

- Trifarotene: New Chemical Entity (NCE)
  - Agonist of retinoic acid receptors (RAR), with particular activity at the gamma subtype of RAR
  - Retinoid indicated for the topical treatment of acne vulgaris

Early Formulation

- Gel:
  - High % of ethanol to ensure adequate physical and chemical stability of Trifarotene
  - Early formulation used in the positive proof of concept (POC) study in subjects with acne

Prototypes

- Creams adapted to the target indication:
  - Substitute most of the ethanol content
  - Reduction of oil phase is best adapted for the treatment of acne
  - Overcome precipitation of trifarotene in the presence of an aqueous phase due to its low water solubility

To-Be-Marketed Formulation

- Trifarotene Cream (AKLIEF®):
  - Efficacy and tolerability demonstrated
  - Limited systemic exposure (high safety margin)

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Trifarotene: Selection of the To-Be-Marketed formulation

- Selection PK tool kit
  - *In vitro* skin permeation studies (IVPT)
  - Clinical phase 1 PK study in healthy volunteers
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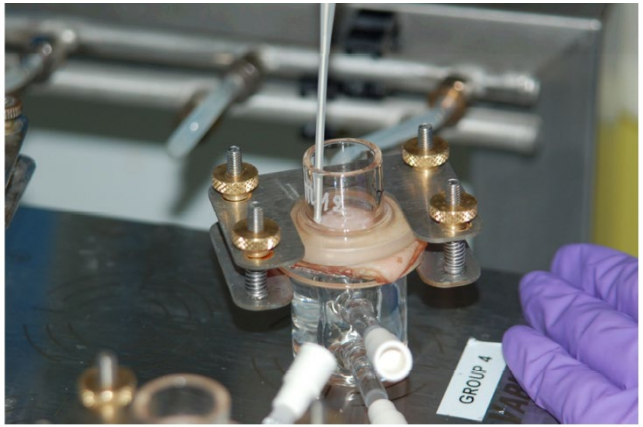
In vitro skin permeation Test (IVPT)

Experimental conditions



- Static diffusion cell
  - 2 cm^2
  - 3 mL receptor fluid
    - Physiological saline solution with nonionic surfactant
    - Sink conditions ➔solubility should not be a limiting factor for diffusion through the skin
  - Skin surface temperature 32°± 1°C

- Human skin
  - Frozen human : Abdominal and breast areas
  - 3 donors
  - Full thickness skin (from 0.71 to 1.82 mm)
  - Skin integrity tested by Trans Epidermal Water Loss (TEWL ≤ 9 $g/m^2/h$)

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In vitro skin permeation Test (IVPT)

Experimental conditions

- Tested formulations
  - Gel used in POC
  - Cream A and Cream B: Alternative to the Gel
  - 50 µg/g
- Application conditions
  - 2 mg/cm^2
  - Application duration: 16 hours
  - Each formulation tested on the same skin donor in duplicate (N=6)
- Trifarotene quantification (LC-MS/MS method)
  - Surface Excess (Mass Balance)
  - *Stratum corneum* (Tape stripping)
  - Epidermis
  - Dermis
  - Receptor fluid

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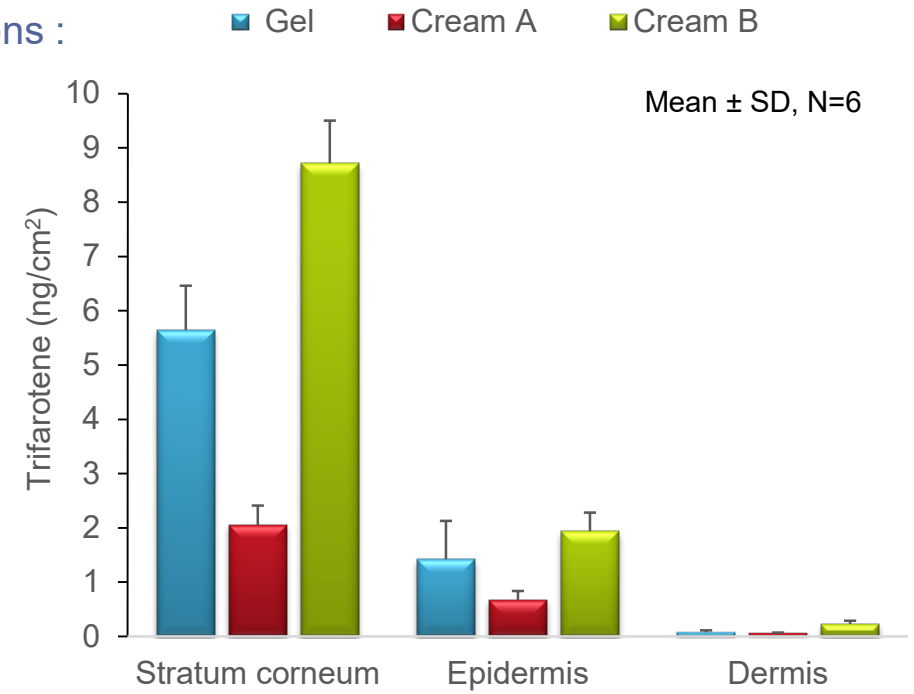
In vitro skin permeation Test (IVPT)

Results *in vitro* Skin penetration

- Similar mass balance between the 3 formulations :
  - > 97 % of the applied dose
- Formulation effect on the Trifarotene total skin penetration
  - Gel : 7 ± 0.8 ng/cm^2 7% of the applied dose
  - Cream A : 3 ± 0.5 ng/cm^2 3% of the applied dose
  - Cream B : 11 ± 0.7 ng/cm^2 11% of the applied dose



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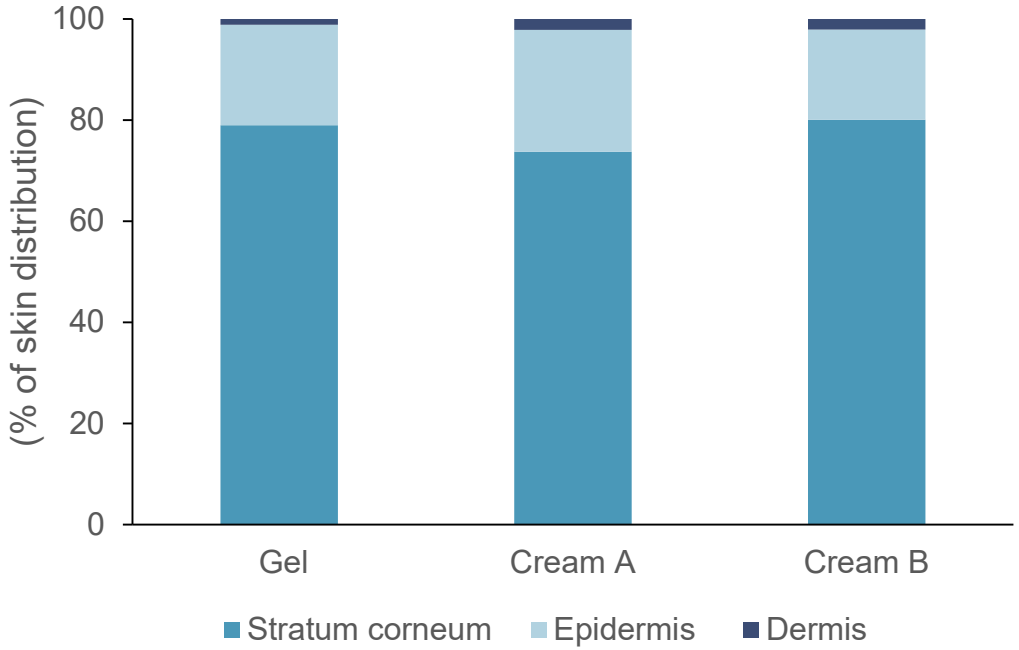
In vitro skin permeation Test (IVPT)

Results Skin Distribution

- No Formulation effect on the Trifarotene skin distribution
  - Exponential skin distribution
  - Trifarotene is mainly distributed in the *stratum corneum*
    - 70 to 80% of the trifarotene skin penetration
  - Low penetration into the dermis
- No trans-cutaneous penetration
  - Trifarotene quantities recovered in the fluid receptor not quantifiable for the 3 formulations



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Trifarotene : From POC to the to-be-marketed formulation

- Selection PK tool kit
  - *In vitro* skin permeation studies (IVPT)
  - Clinical phase 1 PK study in healthy volunteers
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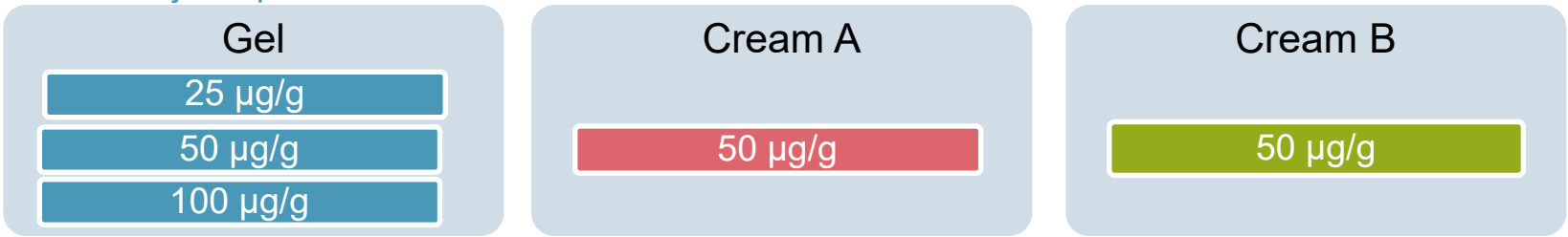
Clinical PK study

Study design

- Healthy volunteers
  - 10 subjects per cohort:



- Application once daily on the face, back and chest for 29 days
  - 2 mg/cm^2 on a fixed surface area
  - All applications performed under controlled conditions
- PK assessments
  - Plasma samples at days 1, 5, 15 and 29
  - Tape stripping and Skin biopsies at day 5

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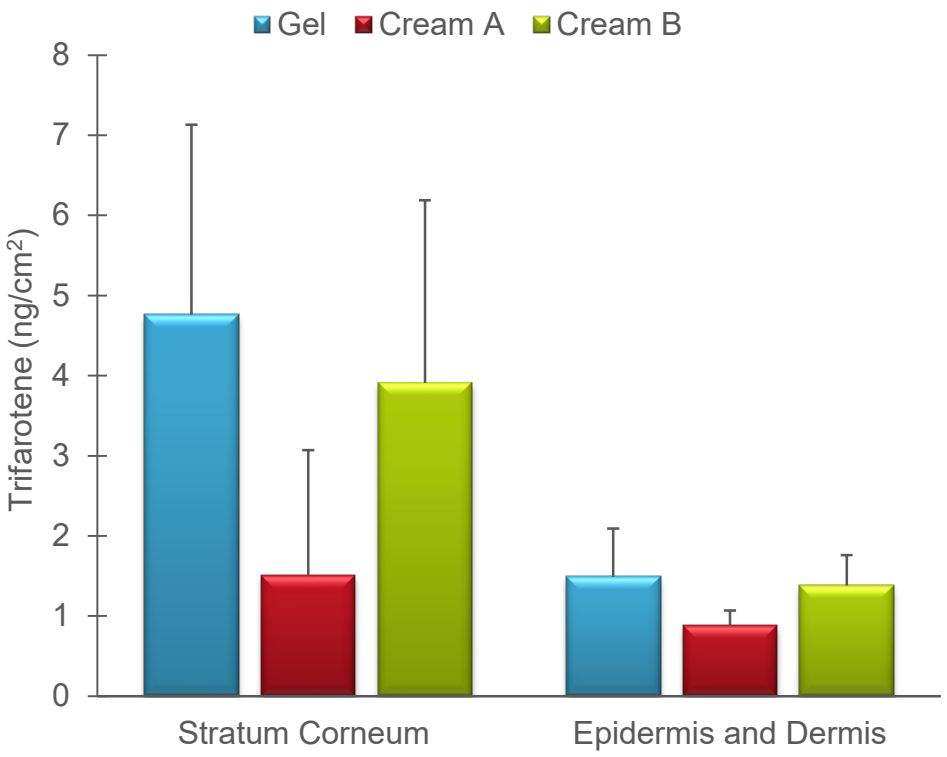
Clinical PK study

Results *in vivo Skin penetration* (Day 5)

- Formulation effect on the total skin penetration
  - Gel : 6 ± 2.6 ng/cm^2
  - Cream A : 2 ± 1.6 ng/cm^2
    - Significant different skin penetration
      3.0 fold lower than Gel
      2.4 fold lower than cream B
  - Cream B : 5 ± 2.7 ng/cm^2
    - No significant difference versus Gel



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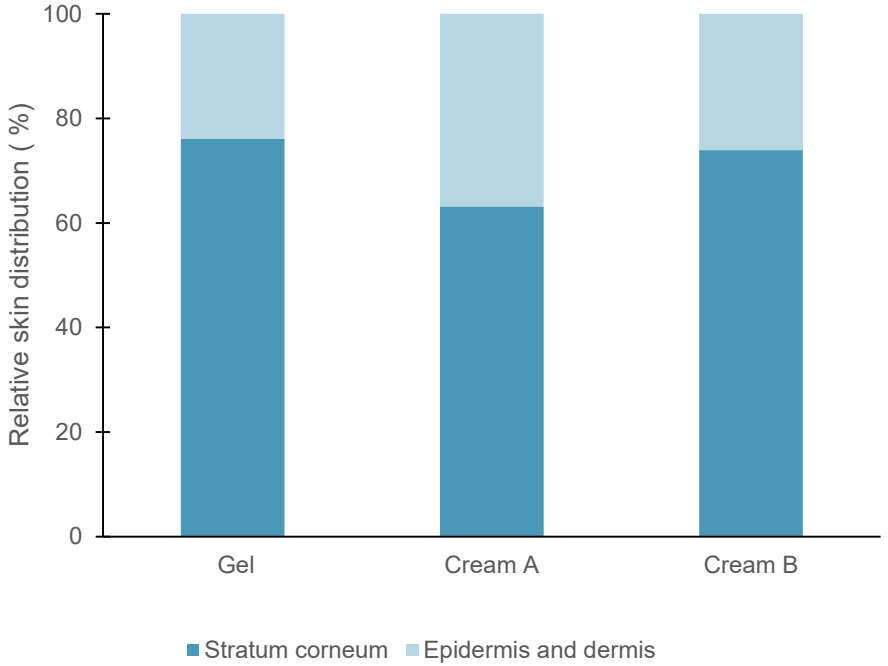
Clinical PK study

Results (Day 5)

- Skin distribution: No clear Formulation effects on the skin distribution
  - Exponential skin distribution
  - Trifarotene is mainly distributed in the *stratum corneum*
    - 60 to 80 % of the total quantity of Trifarotene recovered in skin
- Plasma concentrations ≤ 10 pg/mL for the 3 formulations



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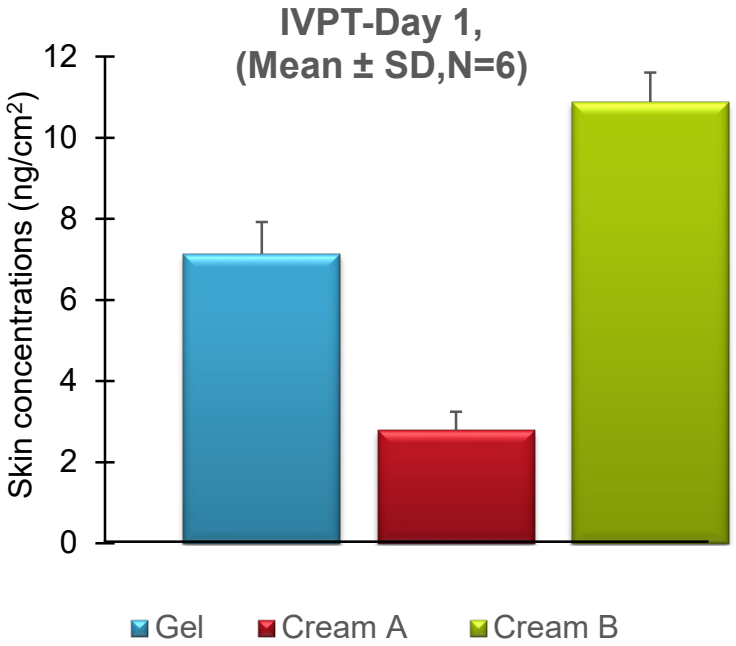
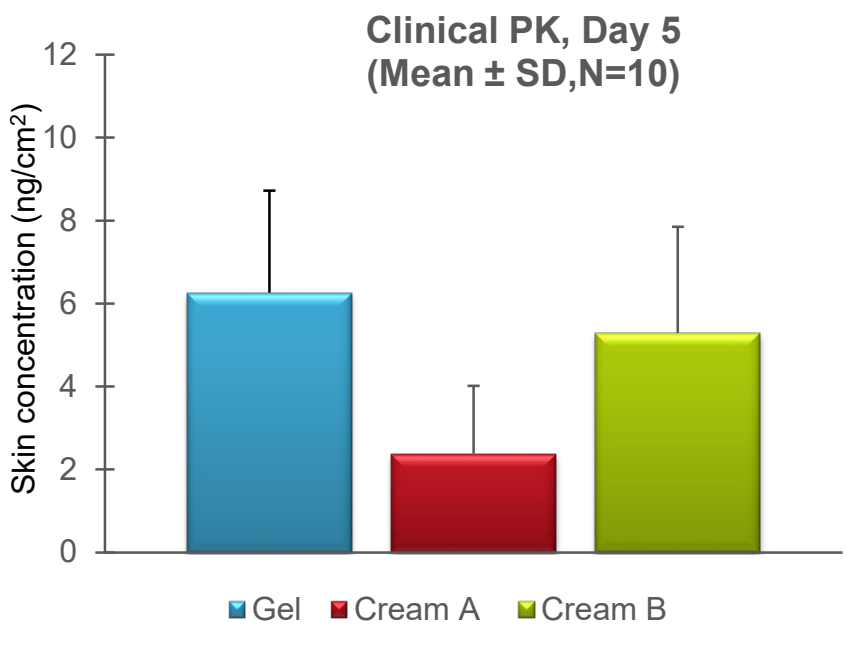
In vitro versus clinical studies





- Predictive value of the IVPT for skin distribution, formulation ranking and total quantities recovered in the skin

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Trifarotene : From POC to the to-be-marketed formulation

- Selection PK tool kit
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  - *Clinical phase 1 PK study in healthy volunteers*
- Clinical proof of efficacy studies in subject with acne

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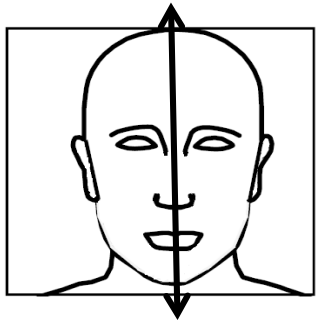
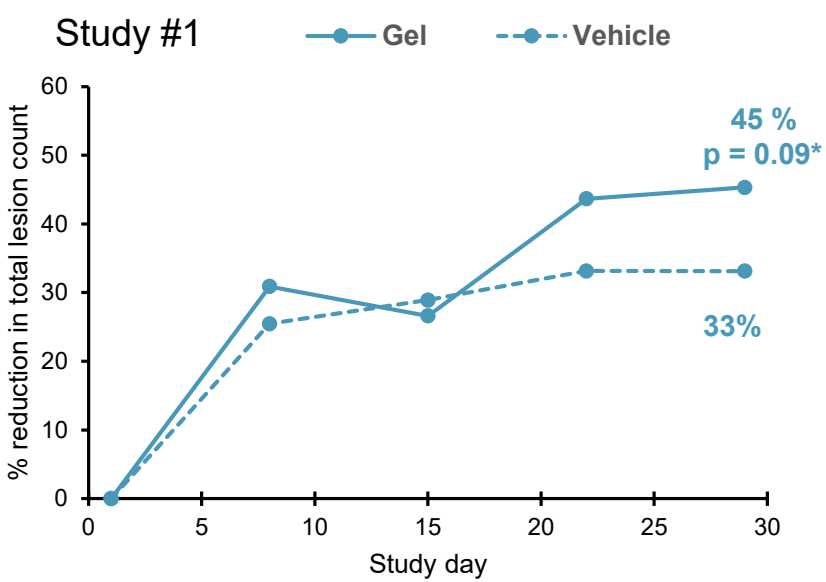
Clinical proof of efficacy studies

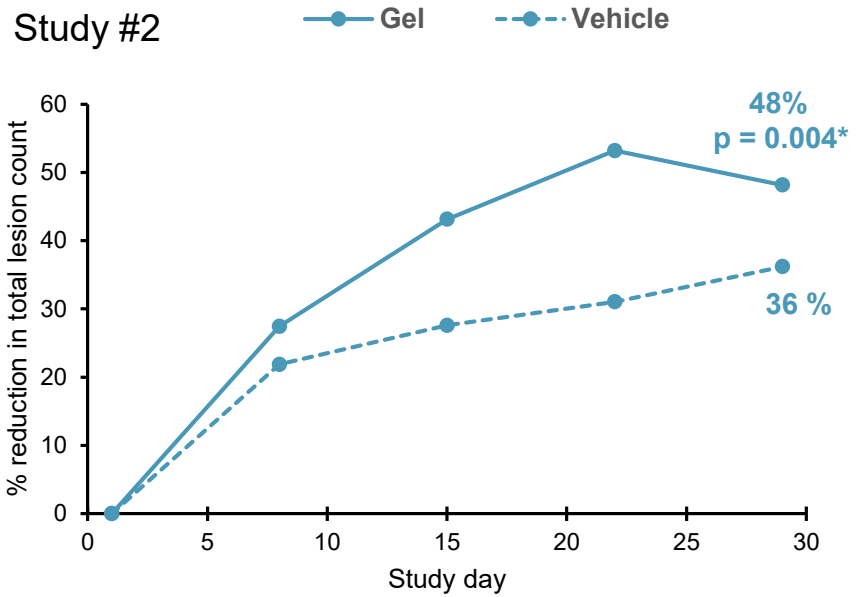
- Patients with moderate to severe acne vulgaris
  - *ca* 20 patients per group
- 2 studies:
  - Intra individual (split face) comparison
  - Study #1:
    - Gel *versus* vehicle
    - Cream A *versus* vehicle
  - Study #2:
    - Gel *versus* vehicle
    - Cream B *versus* vehicle



- 4 weeks once daily application under controlled conditions (2 mg/cm^2)
- Primary clinical endpoint
  - Total acne lesion count and percent reduction of lesion count at week 4

Clinical proof of efficacy studies





- Trifarotene Gel showed significantly different efficacy compared to its vehicle for % reduction in total lesion count in the two studies

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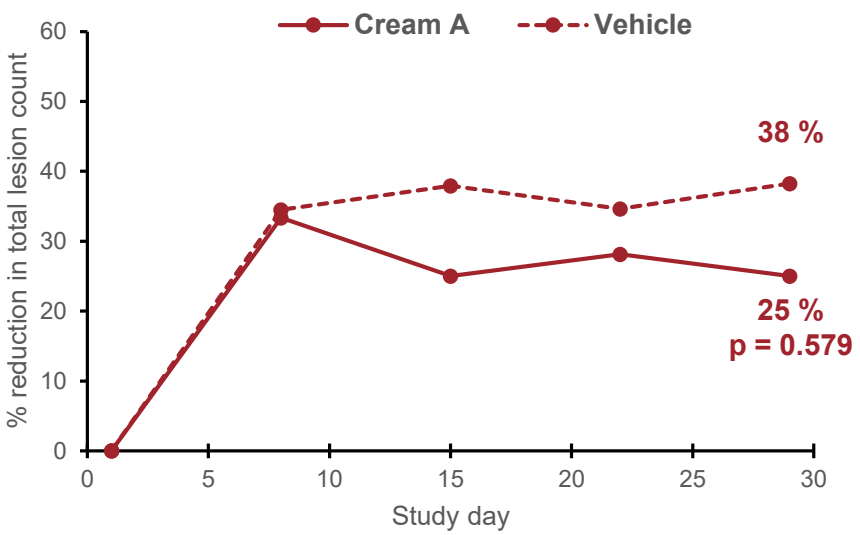
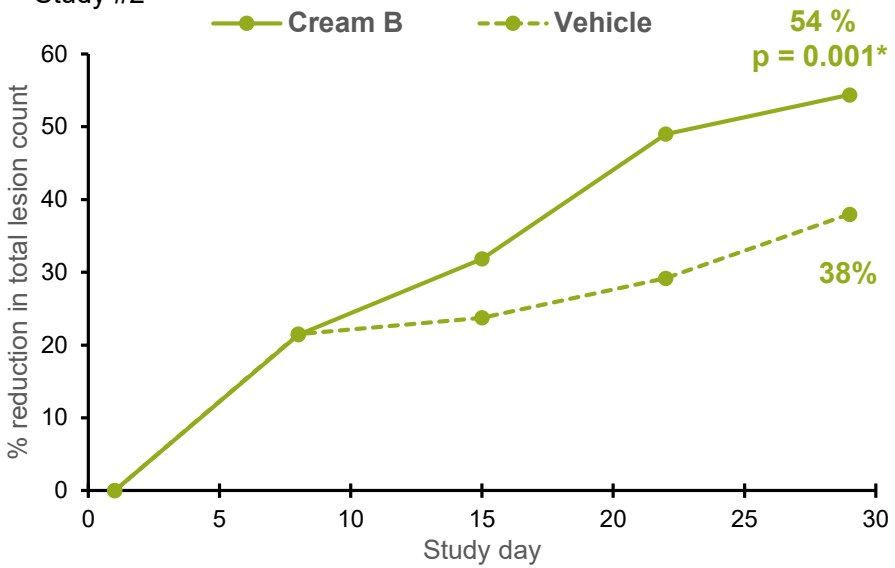
Clinical proof of efficacy studies

Study #1



Study #2



% of reduction in total lesion count

- Cream A showed no significant difference compared to its vehicle
- Cream B showed significantly better results compared to its vehicle

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Conclusion

- IVPT was used as formulation screening tool to compare the skin penetration of trifarotene from different creams *versus* the gel used in the positive POC

- Clinical PK data in Healthy Volunteers were used to confirm the formulation ranking from IVPT

- Clinical data in patients with moderate-to-severe acne were used to assess the clinical use conditions
  - **PK data (blood sample)**: Lesional skin is physiologically different from normal skin and might impact PK profile
  - **Efficacy data**: To confirm the outcome of the POC with the To-Be-Marketed formulation

➢ Cream B (AKLIEF® Cream, 0.005%): Formulation that delivers the right exposure at the target site of action without compromising patient safety

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Take home messages

- IVPT powerful tool for
  - Formulation screening
  - Prediction of the skin penetration and skin distribution
  - PBPK modeling (informative data)
- IVPT powerful tool but
  - Method should be clinically relevant
  - Technical constraints (skin integrity, sink conditions, analytical method, Mass balance ,..)
  - Dose range to be tested
- Communication between experts is instrumental (formulation, *in vitro* and Clinical)
  - Formulation concept and complexity should be acknowledged
  - Clinical skin PK data are needed to confirm the predictability of IVPT and should be generated at the early stage of the project
  - Additional data should be considered, such as efficacy, safety, and skin tolerance
- Caveat :
  - What was observed with trifarotene might not be applicable to other NCE or other skin diseases
  - For NCE, the safety of the to-be-marketed formulation must be confirmed in a Maximal Usage Trial (MUsT)

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Acknowledgments

These slides summarize a collaborative worldwide team effort that has benefited greatly from the input of many people from Galderma

- Non Clinical PK group
- Clinical PK and Bioanalytical groups
- Pharmaceutical group
- Biometry group
- Clinical operation
- Medical expertise

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Questions ?

nathalie.wagner@galderma.com