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

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July 23, 2020
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

- **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)
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

• Clinical proof of efficacy studies in subject with acne
In vitro skin permeation Test (IVPT)

Experimental conditions

• Static diffusion cell
  – 2 cm²
  – 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/m²/h)
**Experimental conditions**

- **Tested formulations**
  - Gel used in POC
  - Cream A and Cream B: Alternative to the Gel
  - 50 µg/g

- **Application conditions**
  - 2 mg/cm²
  - 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/cm²
    7% of the applied dose
  - Cream A: 3 ± 0.5 ng/cm²
    3% of the applied dose
  - Cream B: 11 ± 0.7 ng/cm²
    11% of the applied dose
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 \textit{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
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
- Clinical proof of efficacy studies in subject with acne
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/cm² 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
Clinical PK study

Results *in vivo* Skin penetration (Day 5)

- Formulation effect on the total skin penetration
  - Gel: $6 \pm 2.6$ ng/cm$^2$
  - Cream A: $2 \pm 1.6$ ng/cm$^2$
    - Significant different skin penetration
      - 3.0 *fold lower* than Gel
      - 2.4 *fold lower* than cream B
  - Cream B: $5 \pm 2.7$ ng/cm$^2$
    - No significant difference versus Gel
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
Predictive value of the IVPT for skin distribution, formulation ranking and total quantities recovered in the skin
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*

• **Clinical proof of efficacy studies in subject with acne**
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/cm²)

- Primary clinical endpoint
  - Total acne lesion count and percent reduction of lesion count at week 4
Clinical proof of efficacy studies

Study #1

- Gel
- Vehicle

Study day

% reduction in total lesion count

- 45 %
  - p = 0.09*
- 33%

Study #2

- Gel
- Vehicle

Study day

% reduction in total lesion count

- 48 %
  - p = 0.004*
- 36 %

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

Study #1

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

Study #2

- % reduction in total lesion count
  - Study day 0 to 30
  - Cream A: 38% at study day 0
  - Vehicle: 25% at study day 0
  - p = 0.579

- Study day 0 to 30
  - Cream B: 54% at study day 0
  - Vehicle: 38% at study day 0
  - p = 0.001*

% of reduction in total lesion count
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.
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)
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
Questions?
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