A clinical dermal open flow microperfusion study to assess bioequivalence of topically applied diclofenac products using cutaneous pharmacokinetic endpoints

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Introduction

Pilot and pivotal clinical bioequivalence (BE) studies were conducted to evaluate **capabilities of dermal open flow microperfusion (dOFM) to monitor the cutaneous pharmacokinetics (PK)** of a highly lipophilic and highly protein-bound drug, **diclofenac, for BE assessment.**

Objectives of the pilot study were to

- Optimize parameters for the pivotal study such as topical product dose amount and duration of application,
- Assess the suitability of the study design parameters by monitoring any lateral diffusion between adjacent application sites and measuring systemic drug concentrations that may redistribute to the skin, and
- Evaluate suitability of a non-equivalent test product to be discriminated as a negative control for BE.

The objective of the pivotal study was to evaluate BE based on comparing the cutaneous PK endpoints, including maximum drug concentration ($\mathbf{C_{max}}$) and area under the curve **(AUC**), for the reference gel product (R) and

- A positive BE control: Marketed generic gel product (T_{gen} vs. R)
- A negative BE control : Non-equivalent solution product ($T_{non\text{-}equ}$ vs. R)

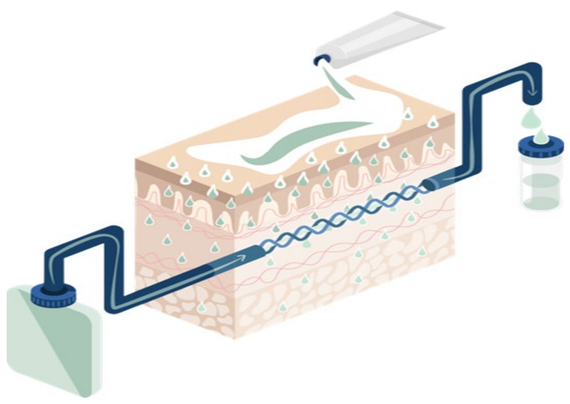

Figure 1: Working principle of the dermal Open flow microperfusion (dOFM)

Methods

- Study design: Single center, open label study with 22 healthy subjects (6 in the pilot and 16 in the pivotal study).
- Study duration: 25 h (1 h pre-dose, 24 h post-dose.)

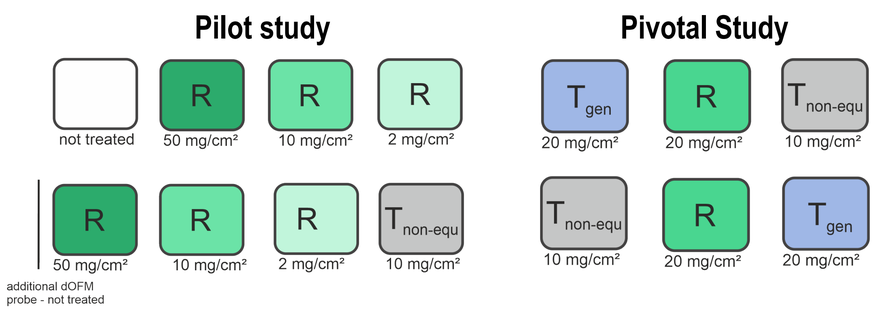

Figure 2: Application schemes of pilot and pivotal study

- Products:
  - Reference gel product (R): Voltaren (diclofenac sodium) topical gel, 1% (GSK, USA)
  - Generic gel product (T_{gen}): diclofenac sodium topical gel, 1% (Perrigo, USA)
  - Non-equivalent solution product ($T_{non\text{-}equ}$): Pennsaid (diclofenac sodium) topical solution, 2% (Horizon Pharma, USA)

Conclusions

- The pilot study showed that the selected study design parameters were appropriate for the pivotal study.
- Results from the pivotal study proved
  - **dOFM can demonstrate BE** between equivalent diclofenac topical products and
  - dOFM was sensitive to **discriminate differences in bioavailability between different formulations** (a diclofenac topical solution versus diclofenac topical gel).

Results

Pilot Study

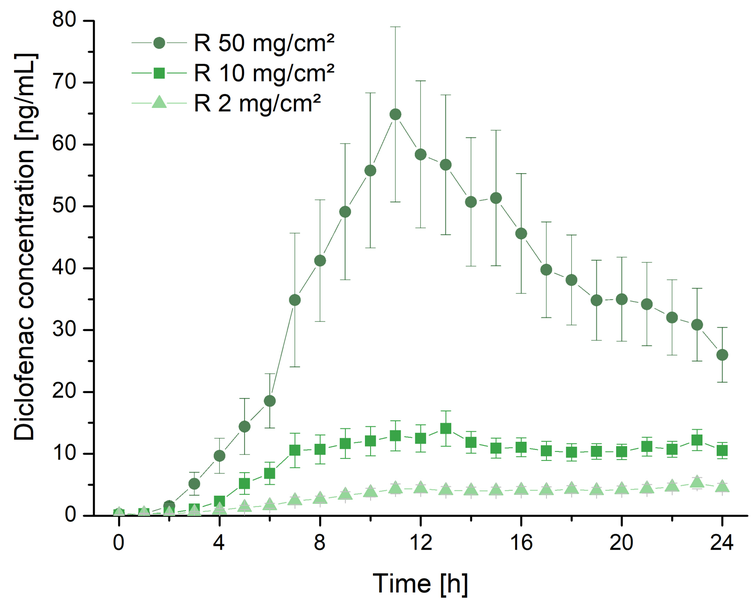

Figure 3: Dermal concentration-time profiles (mean ± SE; 6 subjects, n = 12 thighs) for three different doses of the reference gel product (R).

- **PK endpoints of different doses of R were well differentiated**. With increasing dose (2, 10 and 50 mg/cm²) median PK endpoints increased.
- The low amount of diclofenac in the untreated sites indicated **no significant redistribution of diclofenac or lateral diffusion** from sites treated with R.
  - Negligible amounts of diclofenac were detected in the untreated sites on the arm compared to the treated application sites.
  - Negligible amounts of diclofenac were detected in the untreated dOFM probes positioned next to the treated application sites with R.
- **PK endpoints from $T_{non\text{-}equ}$ were well distinguishable from R and can therefore be used as negative control in the pivotal study.** R and $T_{non\text{-}equ}$ produced significantly different PK endpoints, log AUC_{0to24h} ($p < 0.0001$) and log C_{max} ($p < 0.0001$).
- Results confirmed that the **study design parameters were appropriate** for the pivotal study and a reasonably complete PK profile was captured.

Pivotal Study

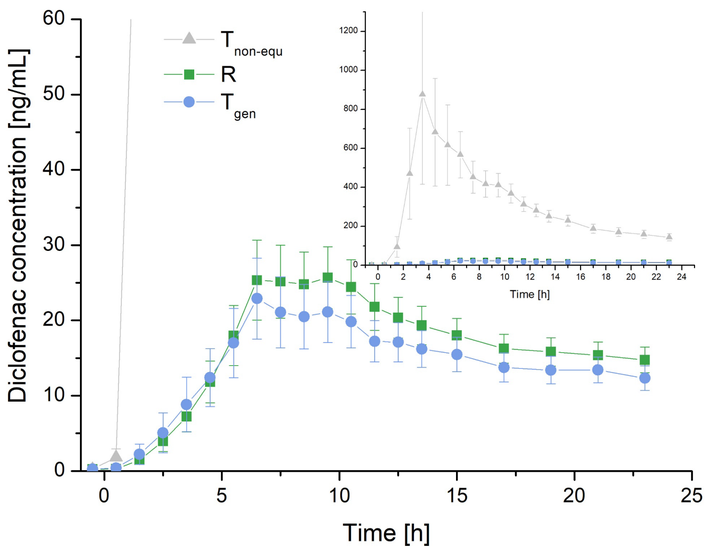

Figure 4: Dermal concentration-time profiles (mean ± SE; 16 subjects, n = 32 thighs) for the non-equivalent solution product ($T_{non\text{-}equ}$), the reference gel product R and the generic gel product T_{gen}.

BE evaluation:

- The T_{gen} product was accurately **found to be bioequivalent** to its reference gel product after exclusion of all data from each application site adjacent to $T_{non\text{-}equ}$, as these data might have been influenced by lateral diffusion of diclofenac from the $T_{non\text{-}equ}$-treated sites to the adjacent R-treated sites.
- The **negative control was sensitively discriminated** and found **not to be bioequivalent** to the reference gel product.

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