A clinical dermal open flow microperfusion (dOFM) study to assess bioequivalence (BE) of different topically applied diclofenac products

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Introduction

In several previously performed clinical studies, the cutaneous sampling technology dermal open flow microperfusion (**dOFM**) has successfully **demonstrated its capability** to accurately and sensitively compare the cutaneous pharmacokinetic (PK) of various topically applied drug products (from hydrophilic to moderate lipophilic and moderate protein-bound drugs) for **bioequivalence (BE) evaluation**.[1,2]

Objectives

To evaluate dOFM's capability to assess BE of **highly lipophilic and highly protein-bound drugs**, we performed a clinical study using several products containing diclofenac sodium.

The **objective of the pilot** study was to

- determine the optimal study design parameters for the pivotal study (dose).
- characterize the influence of potential confounding factors such as lateral diffusion and systemic redistribution.
- evaluate the suitability of a diclofenac sodium topical solution, 2% to serve as negative control.

The **objective of the pivotal study** was to assess BE by comparing the cutaneous PK of the

- reference gel with those from its approved generic gel (positive BE control),
- and those from a non-equivalent solution (negative BE control).

Methods

- Single center, open label, pivotal study with **22 healthy volunteers** (6 in the pilot and 16 in the pivotal study).
- dOFM was used to **continuously sample dermal interstitial fluid** for 25 hours (1 hour pre-dose, 24 hours post-dose)
- Products:
  - **Reference gel (R):** Voltaren (diclofenac sodium) topical gel, 1% (GSK, USA)
  - **Generic gel (T_{gen}):** Diclofenac sodium topical gel, 1% (Perrigo®, USA)
  - **Non-equivalent solution ($T_{non-equ}$):** Pennsaid (diclofenac sodium) topical solution, 2% (Horizon Pharma, USA)
- Topical **application schema** (products were removed after 6 hours):

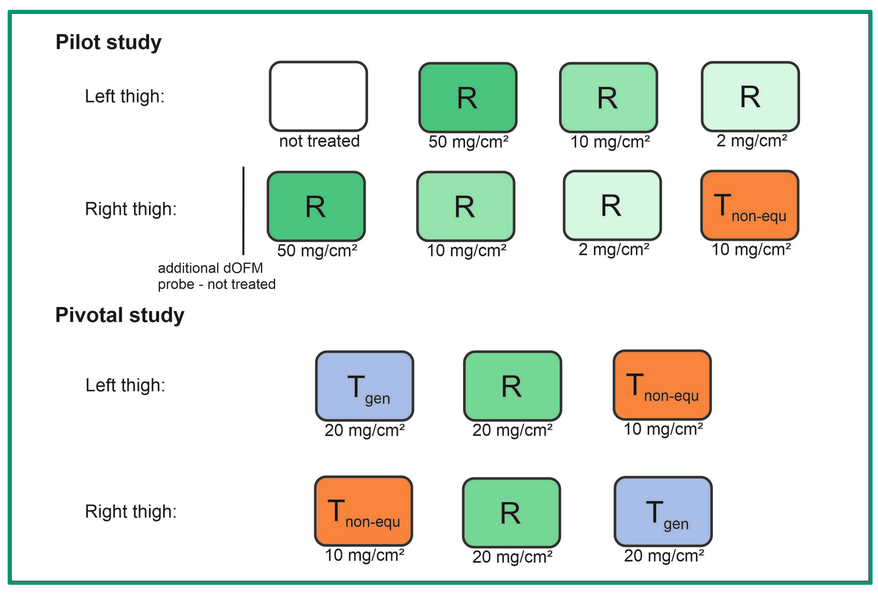

Figure 1: Applied products and doses for the pilot and pivotal studies.

- **BE evaluations:** Scaled average BE (SABE) approach[3]
  Condition for use: within-reference variability $s_{WR} > 0.294$
  - Mixed criterion for BE:
    - 95% upper confidence bound is ≤ 0 and
    - geometric mean ratios (GMR) for PK endpoints lie within the BE limits of 0.8 - 1.25.
- **Preliminary data analysis and anomalous data exclusion:**
  The non-equivalent solution showed an order of magnitude higher diclofenac bioavailability than the gel formulations, causing lateral diffusion of diclofenac to the adjacent dOFM probes at the sites treated with the reference gel. A sensitivity analysis demonstrated that only data from the dOFM probe closest to the adjacent application site (treated with the solution product) on each thigh was affected by lateral diffusion was thus, excluded prior to BE analysis.

Results

- **Pilot study:**
  Results showed that the tested study design parameters were appropriate for the subsequent pivotal study:

Parameter	Results
Dose-PK relationship	With increasing dose (2, 10 and 50 mg/cm²) median PK endpoints increased: • AUC_{0to24h}: 72.70, 167.48 and 584.94 [ng/ml]*h • C_{max}: 5.63, 14.17 and 47.86 ng/mL
Redistribution	Negligible amounts of diclofenac were detected in the untreated sites on the arm compared to the treated application sites and most of the samples were below lowest limit of quantification (LLOQ).
Lateral diffusion	Negligible amounts of diclofenac were detected in the untreated dOFM probes positioned next to the treated application sites with R and most of the samples were below LLOQ.
Negative control	R and $T_{non-equ}$ produced significantly different PK endpoints, log AUC_{0to24h} ($p < 0.0001$) and log C_{max} ($p < 0.0001$).

- **Pivotal study:**
  - **Dermal concentration-time profiles** (mean ± SE, 16 subjects, n = 32 thighs)

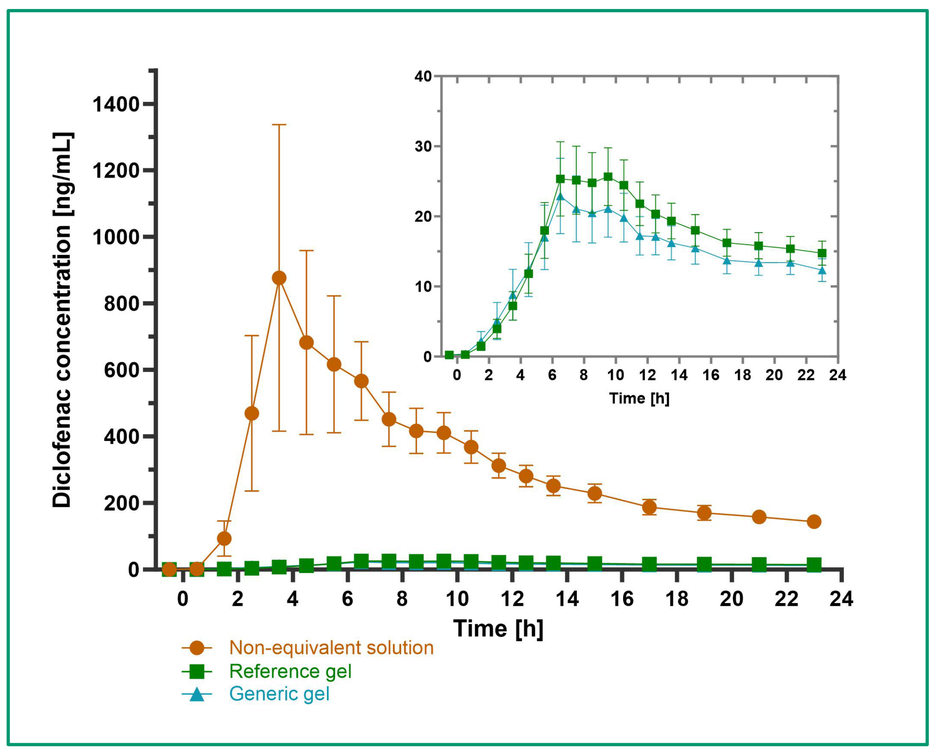

Figure 2: Diclofenac concentration-time profiles for reference gel, generic gel and the solution

- **BE evaluations**: The generic gel product was found to be bioequivalent to its reference gel product (positive control). Negative control was sensitively discriminated and found not to be bioequivalent to the reference gel product (negative control).

Comparison	PK endpoints	Geometric mean ratio	Within-reference standard deviation	95% upper confidence bound	SABE-criterion satisfied
Positive Control (T_{gen} vs. R)	AUC_{0to24h}	0.84	0.44	-0.05	Y
	C_{max}	0.83	0.50	-0.07	Y
Negative Control ($T_{non-equ}$ vs. R)	AUC_{0to24h}	17.46	1.14	8.82	N
	C_{max}	22.42	1.18	10.56	N

Conclusions

These results for diclofenac and those for acyclovir[1], lidocaine and prilocaine[2] indicate that dOFM has the **potential to support a demonstration of BE for a wide range of different topical drug products.** Understanding the potential impact of local crosstalk, in general, and during pilot studies, can help to optimize the study design of pivotal BE studies.

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References

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Unterhalb dieser Linie werden keine Inhalte mehr gesetzt!