A clinical study to assess the bioequivalence of topical diclofenac products using dermal open flow microperfusion

Katrin Tiffner[1], Tannaz Ramezanli[2], Thomas Birngruber[1], Manfred Bodenlenz[1], Felipe Teles[1], Reingard Raml[1], Sonja Kainz[1], Sam G. Raney[2], Frank Sinner[1]

[1]HEALTH – Institute of Biomedicine Research and Technologies, JOANNEUM RESEARCH, Graz, Austria,
[2]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA

Poster number: xxxx

PURPOSE

Pilot and pivotal clinical 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 bioequivalence (BE) assessment.

OBJECTIVES

Objectives of the **pilot study** were to

- optimize parameters for the pivotal study such as the **topical product dose amount** and **duration of application**
- characterize the influence of potential confounding factors such as
  - **lateral diffusion** between adjacent application sites
  - **redistribution** of the drug via systemic circulation into the skin
- evaluate the **suitability** of a diclofenac sodium solution to serve as a **negative control** for BE relative to the reference gel product.

Objectives of the **pivotal study** were to

- evaluate BE based on the cutaneous PK endpoints: maximum drug concentration (C_{max}) and area under the curve (AUC) for the following comparisons:
  - **Positive control for BE:** Marketed generic gel product vs. reference gel product (T_{gen} vs. R)
  - **Negative control for BE:** Non-equivalent solution product vs. reference gel product ($T_{non\text{-}equ}$ vs. R)

METHODS

Study design: Single center, open label study with 22 healthy subjects (6 in the pilot and 16 in the pivotal study).

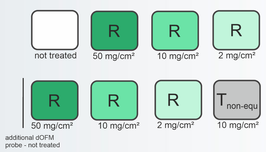
Study duration: dOFM was used to continuously sample interstitial fluid for 25 h (1 h pre-dose, 24 h post-dose)

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)

Application scheme for the left and right thigh:

- Pilot study



- Pivotal study

BE evaluations: Scaled average BE (SABE) approach [1]. Condition for use: $s_{WR} > 0.294$. Mixed criterion for BE:

i. 95% upper confidence bound is ≤ 0 and
ii. geometric mean ratios (GMR) for PK endpoints lie within the BE limits of 0.8 - 1.25.

Review of anomalous data for BE evaluations:

The dermal concentrations of diclofenac at $T_{non\text{-}equ}$ sites were more than 14 times higher than those of R. A review of the data indicated that a diclofenac crosstalk from the $T_{non\text{-}equ}$-treated sites to the adjacent R-treated sites may have occurred. A sensitivity study was performed to evaluate how inclusion or exclusion of one of the three dOFM probes that is located closest to the $T_{non\text{-}equ}$-treated site may influence an assessment of BE.

RESULTS

Pilot study

Results confirmed that the **study design parameters** were **appropriate** for the pivotal study and a reasonably **complete PK profile** was captured.

Pivotal study

The **generic gel product** was found to be **bioequivalent** to its reference gel product after exclusion of anomalous data. **Negative control** was **sensitively discriminated** and found not to be bioequivalent to the reference gel product.

CONCLUSIONS

1. The pilot study showed that the selected **study design parameters** were **appropriate** for the pivotal study.

2. The pivotal study showed that dOFM can **demonstrate BE between equivalent diclofenac topical products** and that dOFM was sensitive to **discriminate differences** in bioavailability between different formulations (diclofenac sodium topical gel versus diclofenac sodium topical solution).

FUNDING

This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of grants (U01FD005861) totaling $ 2,000,000 with 70 percent funded by FDA/HHS. The views are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.

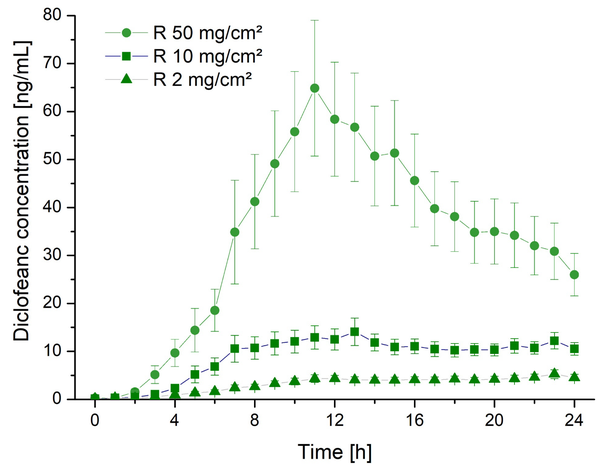
[1] FDA, "Guidance for Industry: Statistical Approaches to Establishing Bioequivalence," Guid. Ind., 2001.

dOFM monitors **cutaneous bioavailability** of different diclofenac products for **BE evaluations**

PILOT STUDY

Dermal PK profiles for the three different doses

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



Study design parameters were appropriate

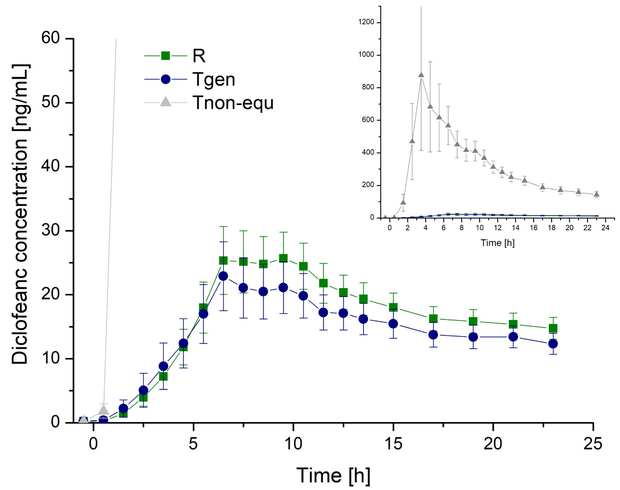
PK endpoints of different doses of R were well differentiated. The low amount of diclofenac in the untreated sites indicated no significant redistribution of diclofenac or lateral diffusion from sites treated with R. PK endpoints from $T_{non\text{-}equ}$ were well distinguishable from R and can therefore be used as negative control in the pivotal study.

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 $T_{non\text{-}equ}$ produced significantly different PK endpoints, log AUC_{0to24h} ($p < 0.0001$) and log C_{max} ($p < 0.0001$).

PIVOTAL STUDY

Dermal PK profiles for the three products

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



BE analysis for the positive control and negative control

After exclusion of anomalous data the SABE criteria were satisfied for the positive control. The non-equivalent solution product ($T_{non\text{-}equ}$) was not found to be bioequivalent to reference gel product (R) according to SABE criteria.

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 ($T_{non\text{-}equ}$ vs. R)	AUC_{0to24h}	17.462	1.14	8.82	N
	C_{max}	22.421	1.18	10.56	N

CONTACT INFORMATION: frank.sinner@joanneum.at