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Dermal pharmacokinetic endpoint studies to evaluate bioequivalence of topically applied lidocaine and prilocaine drug products

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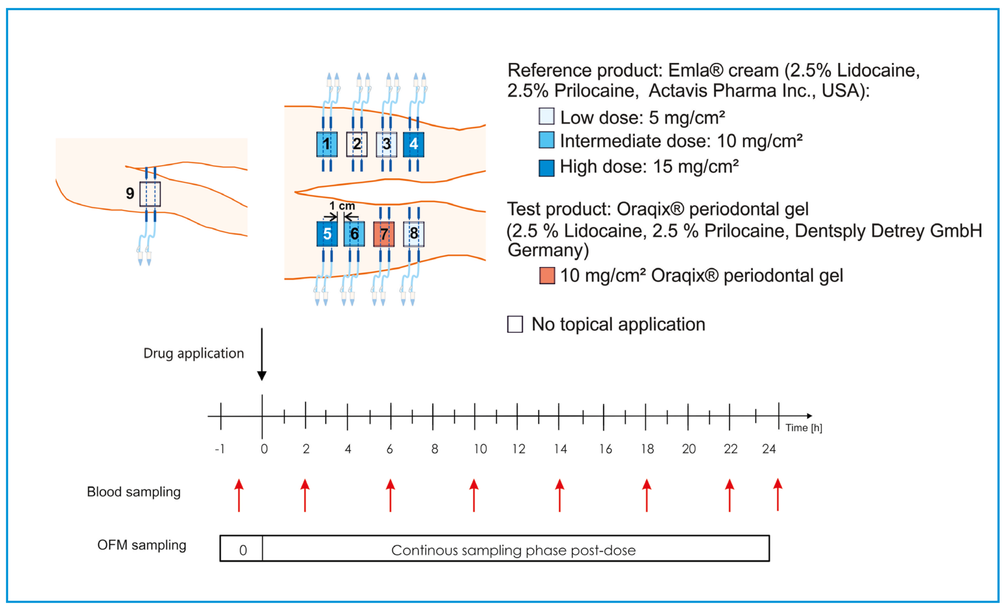
Introduction

A promising approach to evaluate bioequivalence (BE) of topical dermatological drug products compares the in vivo dermal pharmacokinetic (PK) profiles for a prospective generic product and its reference listed drug (RLD) product using dermal open flow microperfusion (dOFM). The feasibility of dOFM to evaluate BE was previously demonstrated for acyclovir creams [1]. The objective of the current study is to assess the feasibility of dOFM to evaluate the BE of drugs that are more hydrophobic and more protein-bound than acyclovir. The specific aim of the current pilot study is to evaluate the dermal PK of lidocaine (moderately hydrophobic, moderately protein-bound) and prilocaine (moderately hydrophobic, highly protein-bound) topical products using dOFM, and to verify/optimize the parameters to be applied in a subsequent pivotal in vivo BE study by:

- Characterization of the **dose response relationship** of three different doses of the reference product, EMLA® topical cream (2.5% lidocaine, 2.5% prilocaine)
- Evaluation of the suitability of Oraqix® periodontal gel (2.5% lidocaine, 2.5% prilocaine) to serve as a **negative control for BE** relative to the reference cream product.
- Investigation of the influence of **potential confounding factors** such as lateral "cross-talk" between adjacent test sites, or redistribution of the drug back into the skin by the systemic circulation.

Methods

- Single center, open label pilot study
- 6 healthy subjects
- Study duration: 25 hours (1 hour pre-dose and 24 hours post-dose)
- Applied products, dosing (at 9 test sites) and sampling schedule:



- Sample analysis: High performance liquid chromatography (HPLC) tandem mass spectrometry (MS/MS) analysis (LLOQ: 1 ng/mL)
- BE statistics (reference cream versus Oraqix® periodontal gel):
  - Dermal PK endpoints: Area under the concentration-time curve (AUC) and peak concentration (C_{max})
  - For BE, the calculated 90% confidence interval of the mean ratios of the Oraqix® periodontal gel and reference cream must fall within the BE limits of 0.8 - 1.25 for both PK endpoints (ABE statistical approach).

Results

- **Dose response relationship:** The reference cream product showed a dose-dependent response, confirming that dOFM was sensitive to changes in the bioavailability (BA) of lidocaine and prilocaine (Figure 1).

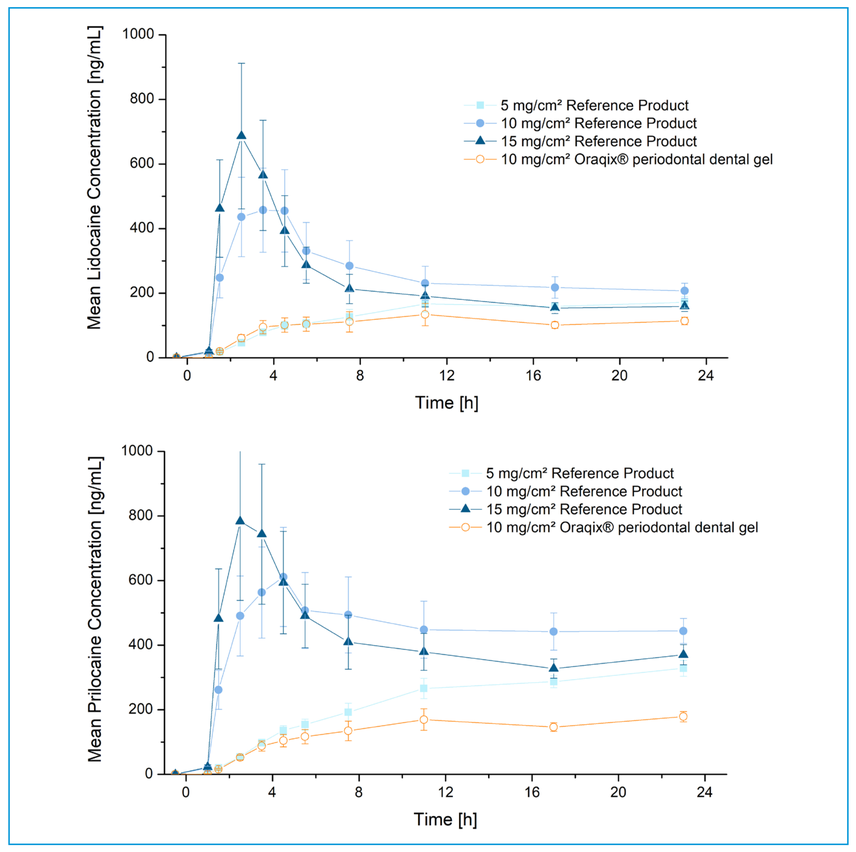


Figure 1: *Mean lidocaine (upper panel) and mean prilocaine (lower panel) concentration-time profiles (±SE, n=6) for three different doses of the reference product and for Oraqix® periodontal gel*

- **Negative Control:** At the same product dose of 10 mg/cm², the AUC values for the Oraqix® gel ($AUC_{Lidocaine}$: 2,444 ng*h/mL; $AUC_{Prilocaine}$: 3,218 ng*h/mL) were well differentiated from those of the reference cream product ($AUC_{Lidocaine}$: 6,036 ng*h/mL; $AUC_{Prilocaine}$: 10,520 ng*h/mL). The 90% confidence interval of the mean ratios did not fall within the BE limits of 0.80–1.25 (Table 1) for both PK endpoints, suggesting that the Oraqix® gel may represent a reasonable negative control for BE with respect to the reference cream product.

Table 1: *Calculated BE limits (the 90% confidence interval of the mean AUC_{0-24} and C_{max} ratios) for the comparison of the reference product with the Oraqix® periodontal gel, both dosed with 10 mg/cm². BE limits were calculated for both lidocaine and prilocaine.*

	PK Endpoint	Calculated BE Limits
Lidocaine	AUC_{0-24}	1.51 – 2.64
	C_{max}	1.75 – 3.21
Prilocaine	AUC	2.14 – 3.63
	C_{max}	2.15 – 3.51

- **Potential confounding factors:** Dermal concentrations from the non-dosed sites on the thigh were below 5 ng/mL for lidocaine and below 16 ng/mL for prilocaine indicating the "cross-talk" between adjacent test sites is negligible. Additionally, no detectable levels of lidocaine and prilocaine were found in dOFM samples from the non-dosed site on the arm, nor in the blood samples. Therefore, with the suggested study design will exclude BE-confounding effects based on systemic redistribution of drugs into the dermis.

Conclusion

The results of this pilot study supported the sensitivity and reproducibility of in vivo dOFM to characterize the dermal PK profiles of lidocaine and prilocaine for BE evaluations. Since Oraqix® gel delivered substantially less lidocaine and prilocaine than the reference cream product, the gel may serve as stuibable negative control for the purpose of this exploratory study. The absence of potential confounding factors indicates that each dOFM probe can monitor and sample rate and extent of lidocaine and prilocaine's bioavailability locally without interference from different treatments at other sites.

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Reference

[1] Bodenlenz, M. et al. 2016. "Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence." Clinical Pharmacokinetics 56(1):1–8.