# Clinical study to assess the cutaneous bioequivalence of topically applied lidocaine and prilocaine products using dermal open flow microperfusion

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Bioequivalence (BE) evaluations based on the cutaneous pharmacokinetics of topically applied drug products that act locally in the skin can be challenging as only a few established methods exist to evaluate the local drug bioavailability. Dermal open flow microperfusion (dOFM) is a reliable method to continuously sample drug concentrations in the dermis, and thus, to assess the rate and extent to which a drug becomes available at or near the site of action. dOFM has been previously used to evaluate the BE of a hydrophilic molecule, acyclovir from two cream products[1].

The current clinical dOFM BE study with 20 healthy subjects aimed to assess whether dOFM can be used to evaluate the cutaneous (dermal) pharmacokinetics and topical BE of drugs that are moderately lipophilic and at least moderately protein-bound, which would be representative of many topical drugs. Products containing a fixed combination of lidocaine and prilocaine were selected for this study. The bioavailability of a reference (R) product, EMLA® (lidocaine and prilocaine) topical cream, 2.5%; 2.5% was compared to itself as a verification (positive control) for BE and was also compared to an approved generic lidocaine and prilocaine topical cream, 2.5%; 2.5% ($T_{generic}$) product as an independent verification (positive control) for BE. Oraqix® (lidocaine and prilocaine) periodontal gel, 2.5%; 2.5% ($T_{non\text{-}equ}$) was selected as a negative control for BE, because it contains the same two drugs in the same concentrations within a substantially different formulation compared to the R product. Each of the subjects received the three drug products in parallel on adjacent application sites on both thighs.

By using a scaled average BE approach, we demonstrated that the reference product 1) was bioequivalent to itself (R vs. R) and to the generic cream product (R vs. $T_{generic}$) and 2) was not bioequivalent to the negative control (R vs. $T_{non\text{-}equ}$).

These results indicate that dOFM can reproducibly verify the BE of a product to itself, accurately establish the BE of an approved generic product to its R product, discriminate the rate and extent of lidocaine and prilocaine bioavailability from products with different formulations, and evaluate the topical BE of lipophilic and protein-bound drug products. These data corroborate the results from a previous dOFM study with topical acyclovir products[1)] and suggest that dOFM has the potential to assess BE for a range of different topical drug products.

1) M. Bodenlenz *et al.*, "Open flow microperfusion as a dermal pharmacokinetic approach to evaluate topical bioequivalence," *Clin. Pharmacokinet.*, vol. 56, no. 1, pp. 91–98, Jan. 2017.

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