Dermal Open Flow Microperfusion

JOANNEUM RESEARCH HEALTH

Continuous Skin Sampling Methods for the Assessment of Cutaneous PK-Based Bioequivalence

Katrin I. Tiffner, Beate Boulgaropoulos, Thomas Birngruber, Manfred Bodenlenz, Bettina C. Lackner, Reingard Raml, **Frank Sinner**

Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development, 3rd November 2022

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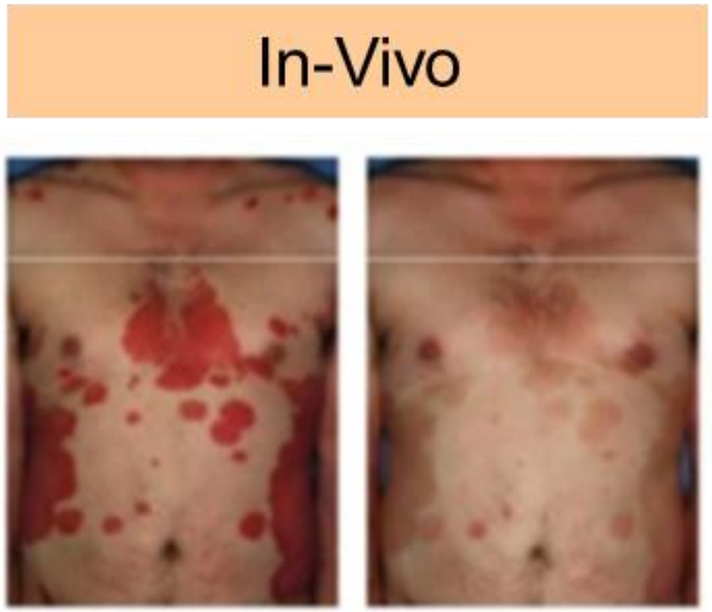
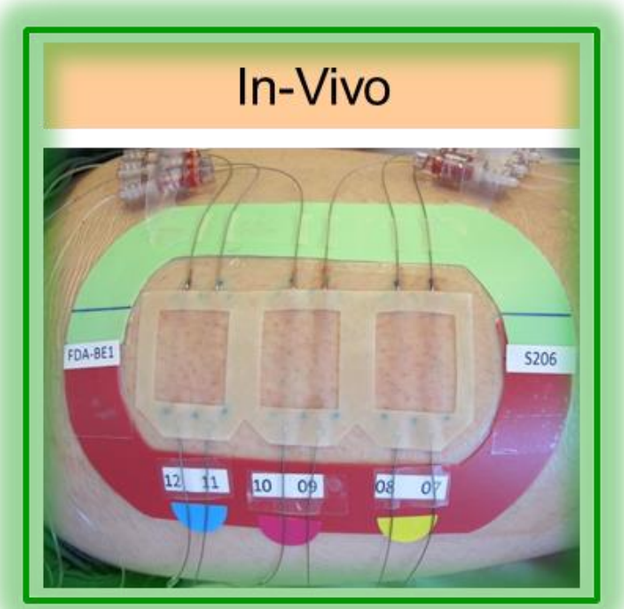
Introduction

- ✓ **optimizing Open Flow Microperfusion for cutaneous bioequivalence**
- ✓ **generating scientific body of evidence for the use of dOFM for BE**



Comparative Endpoint BE Studies

2013 - today



Skin PK-based BE Studies

A big thanks to…

Anita Eberl
Analytics

Katrin Tiffner
dOFM BE Study

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dOFM BE Study

Reingard Raml
Analytics

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Statistics

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OFM Group Leader

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Scientific Writing

Bettina Lackner
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…and many other from different organizations….

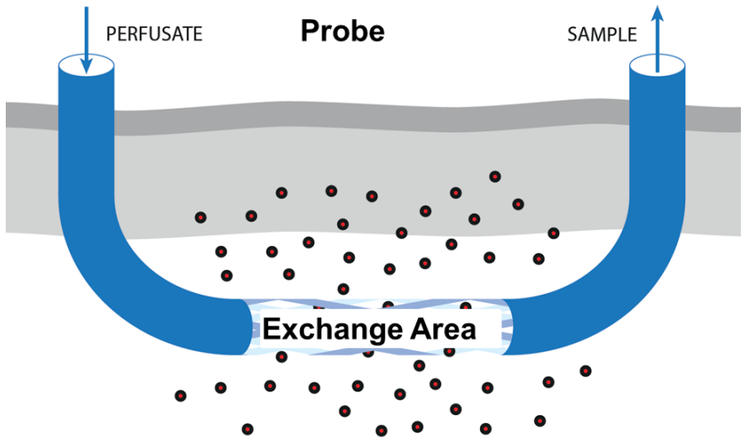
…and many more from our team….

Requirements of skin PK-based BE Methods

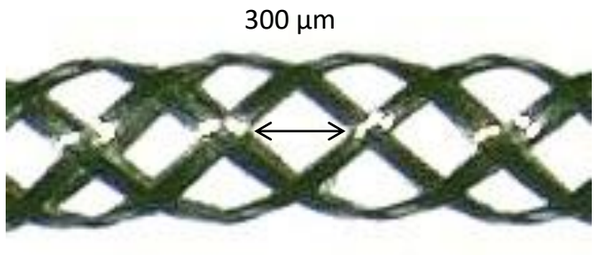
- **Determine cutaneous PK of a topically applied drug at or near the site of action in the dermis**
- **Reproducibility and accuracy of PK-based method**
  - Standardization of equipment and clinical study performance
  - Reflect changes in skin bioavailability (BA)
- **Verification of suitability of skin PK-based clinical study design**
  - General set-up: application of dose, specific dose duration and sampling duration, assessment of absorption and elimination phase (sampling duration of ≥ 12 hours), etc.
  - Verify sensitivity of skin PK-based method
  - Absence of lateral cross-talk between application sites and skin re-absorption from systemic compartment
- **Verification of suitability of dOFM for different classes of topical drugs**
  - Low hydrophobic and low protein-bound: acyclovir
  - Medium hydrophobic and medium protein-bound: lidocaine/prilocaine
  - Highly hydrophobic and highly protein-bound: diclofenac
- **Commercial availability of clinical study performance**

Cutaneous PK of Topically Applied Drugs

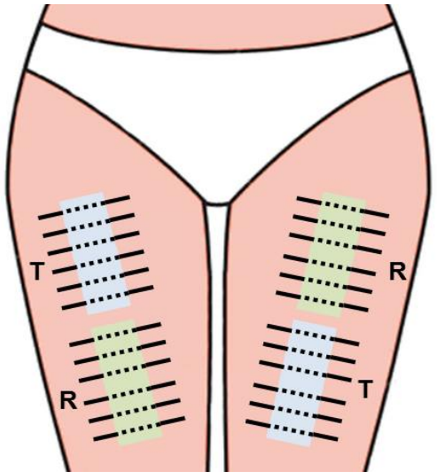
✓ **Dermal Open Flow Microperfusion give access to drug bioavailability.**



Continuous Skin Sampling



Dermal Open Flow Microperfusion



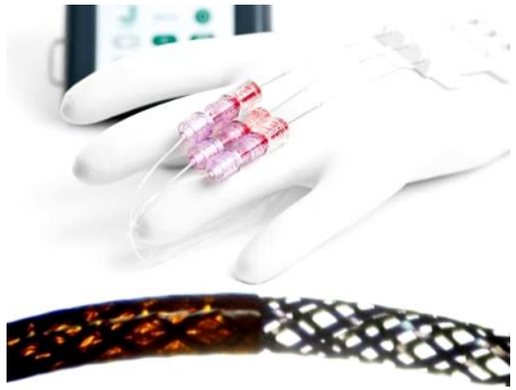
Head-to-Head Comparison

Reproducibility and Accuracy of PK-based Methods

✓ **Required certified dOFM equipment for clinical use**

BE probe

- 0.5 x 15 mm sampling mesh
- 0.5 mm insertion needle
- CE-certified
- patent granted



dOFM Perfusate

- physiological saline solution
- 1% human serum albumin
- and additional substances

MPP pump

- wearable
- 0.1 – 10 µl/min
- 3 OFM probes
- delta push-pull
- CE-certified

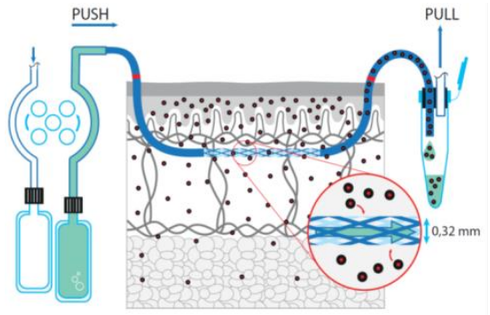
Auxiliary Consumables

- Stabilization ring
- Connectors
- ....

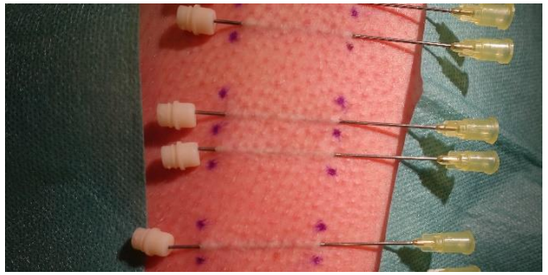
Reproducibility and Accuracy of PK-based Methods

✓ **Rigorous standardization by using SOPs is crucial for PK-based BE**

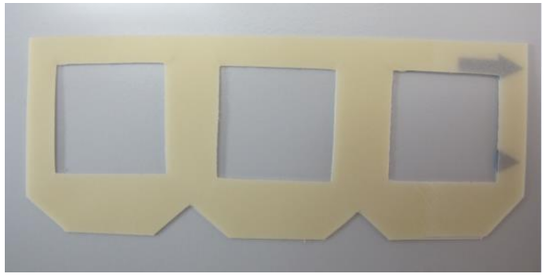
Standardization of dOFM clinical trials



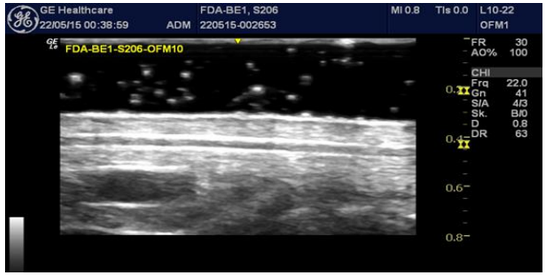
Insertion of probes
Trauma formation
Application site
Dosage application
Probe depth
Flow rate



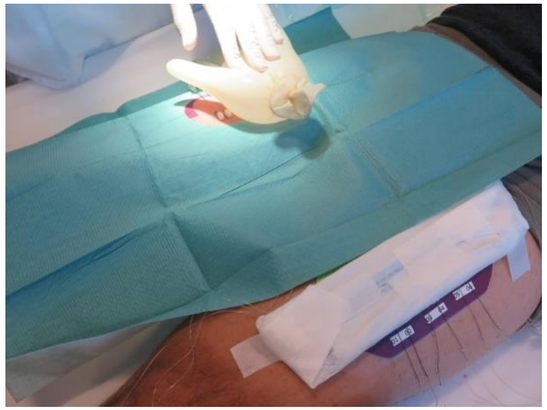
Standardized probe insertion



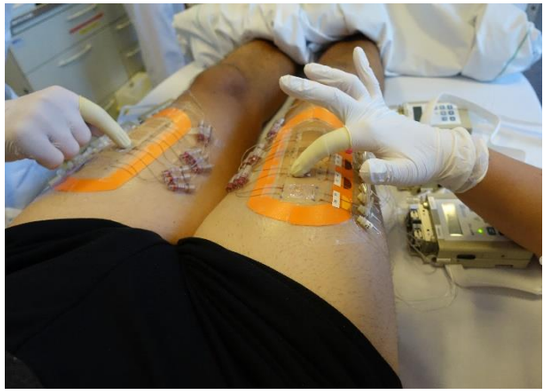
Use of application templates



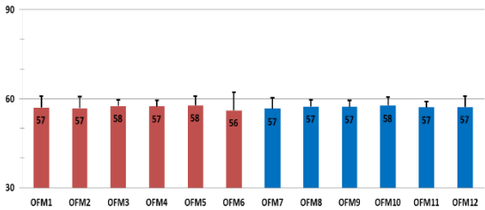
Verification probe depth by ultrasound



Minimization of trauma formation by cooling after probe insertion



Standardized drug application



Flow rates of all probes in one subject

Verification of stable flow by weight measurement

Reproducibility and Accuracy of PK-based Methods

✓ **dOFM showed dose dependency of skin bioavailability.**

Number of healthy subjects	Dose topically applied	Product	API	Total number of application sites	AUC MEAN ($ng*h*ml^{-1}$)	AUC STD
2	5 mg/cm²	US Zovirax®	acyclovir	4	10.4	12.4
2	15 mg/cm² ↑	US Zovirax®	acyclovir	4	50.1 ↑	19.2
6	5 mg/cm²	Emla® Cream	lidocaine	12	3,190.33	1,358.34
6	15 mg/cm² ↑	Emla® Cream	lidocaine	12	5,595.50 ↑	4,800.96
6	5 mg/cm²	Emla® Cream	prilocaine	12	5,390.58	1,773.87
6	15 mg/cm² ↑	Emla® Cream	prilocaine	12	9,687.38 ↑	7,087.91
6	2 mg/cm²	Voltarene	diclofenac	12	63.99	1.75
6	50 mg/cm² ↑	Voltarene	diclofenac	12	680.58 ↑	1.94

Acyclovir (topical) 36 hours
➔ 5 mg/cm² versus 15 mg/cm²

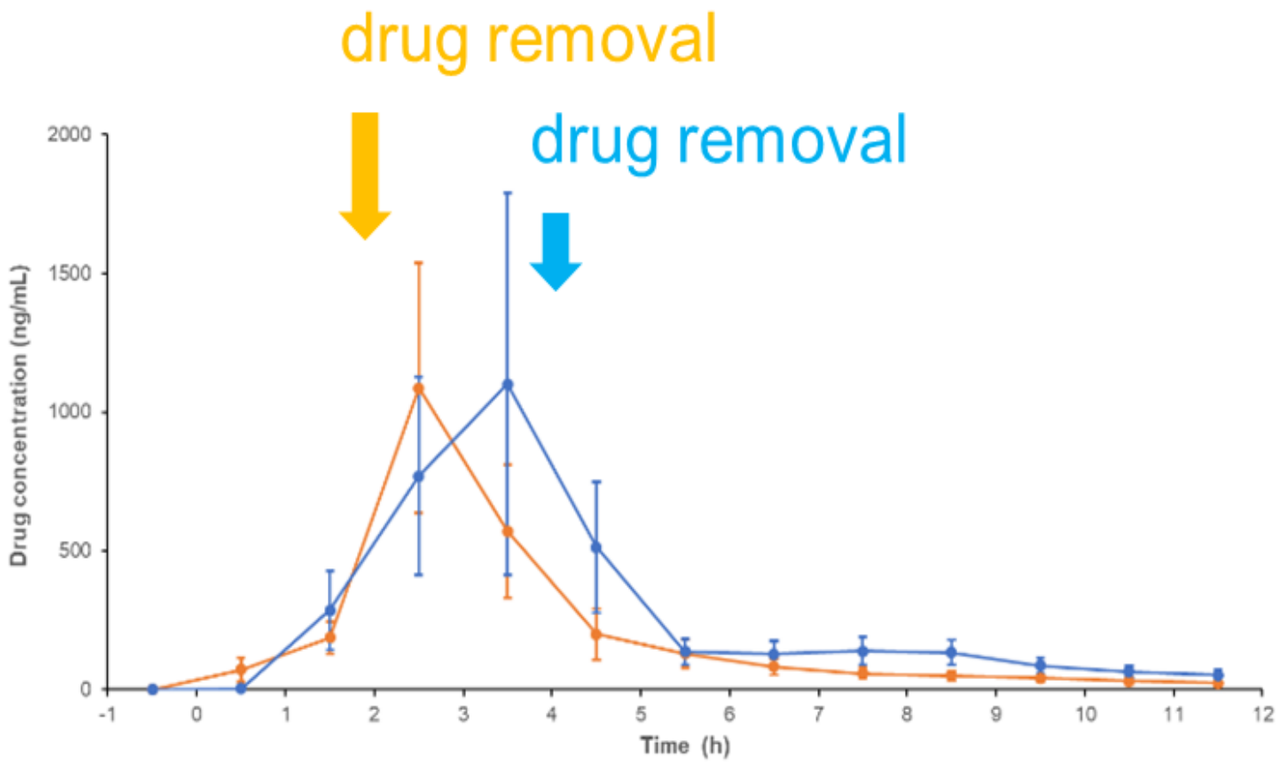
Lidocaine (topical) 24 hours
➔ 5 mg/cm² versus 15 mg/cm²

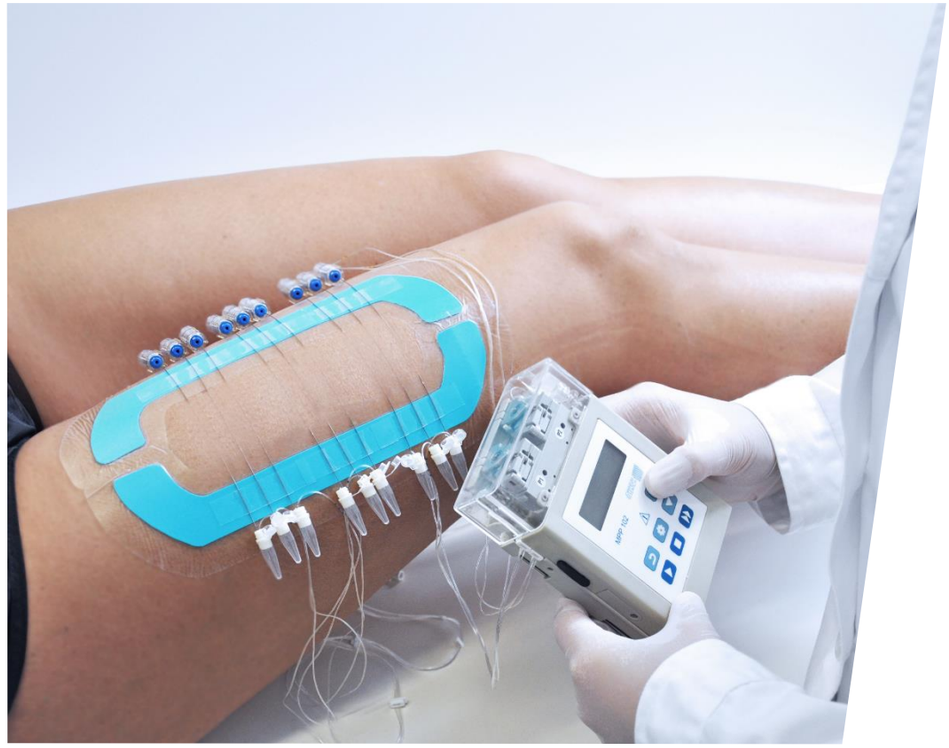
Prilocaine (topical) 24 hours
➔ 5 mg/cm² versus 15 mg/cm²

Diclofenac (topical) 24 hours
➔ 2 mg/cm² versus 50 mg/cm²

Reproducibility and Accuracy of PK-based Methods

✓ **dOFM showed application time dependency of skin bioavailability.**





Lidocaine concentration-time profiles (mean ± SE) for drug product removal after two hours (orange curve) and after four hours (blue curve)

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  - Low hydrophobic and low protein-bound: acyclovir
  - Medium hydrophobic and medium protein-bound: lidocaine/prilocaine
  - Medium hydrophobic and medium protein-bound: diclofenac
- **Commercial availability of clinical study performance**

Suitability of Skin PK-based Clinical Study Design

✓ **A skin PK-based BE study may include three studies.**

Matrix study →

- **Sampling of dermal ISF for analytical method validation (n~6)**

Pilot BE study →

- **Verify suitability of pivotal study design to investigate skin BE (n~8)**
  - Verify dose applied, application time and concentration range of analytical method
  - Verify sensitivity of study design to address skin BA
    - Lower dose is reflected by lower skin BA.
    - Higher dose is reflected by lower skin BA.
  - Absence of lateral cross-talk between application sites
  - Skin re-absorption from systemic compartment

Pivotal BE study →

- **Investigate equivalence of generic drug to RLD (n~20)**

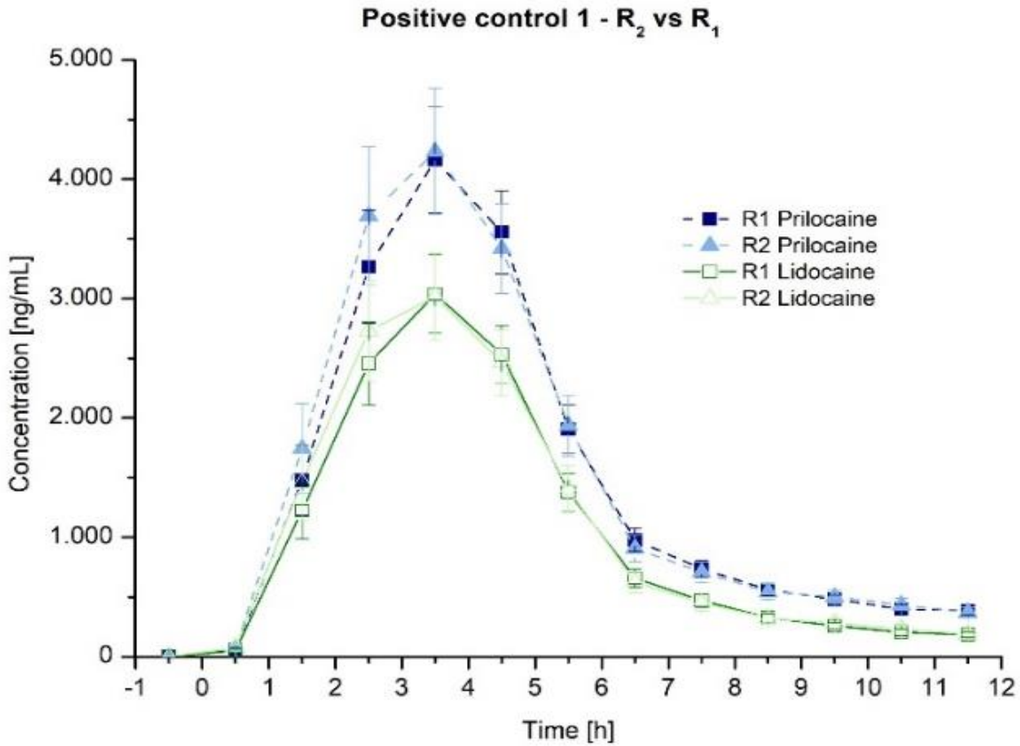
Suitability of Skin PK-based Clinical Study Design

✓ **Clinical design is suitable for pivotal dOFM BE study.**

Pilot Study:

Verify dOFM clinical study design

- ✓ A suitable PK profile including absorption, elimination phase and C_{max} of both APIs was obtained.
- ✓ The concentration range of the analytical method (HPLC-HiResMS) of 1 ng/mL for analytical validation was confirmed.



Skin bioavailability of EMLA® by dOFM

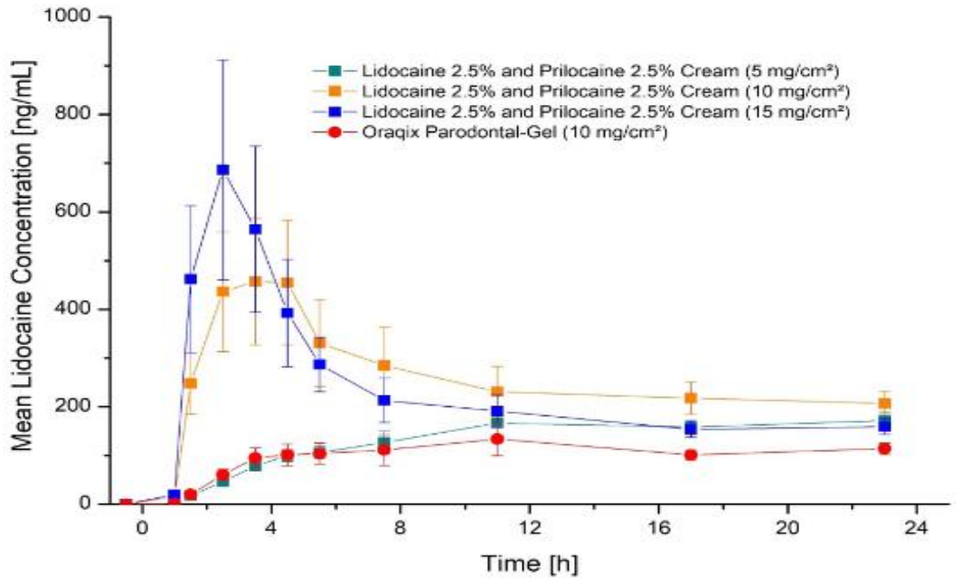
Suitability of Skin PK-based Clinical Study Design

✓ **Clinical design is suitable for pivotal dOFM BE study.**

Pilot Study:

Verify dOFM clinical study design

- ✓ Verified sensitivity of study design to address skin BA.
  - ✓ Dose response from 5 < 10 < 15 mg/cm^2 for AUC and C_{max}
  - ✓ Oraqix® showed different skin BA than EMLA® at same dose.

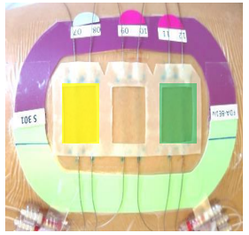


Skin bioavailability of EMLA® and Oraqix® by dOFM

Suitability of Skin PK-based Clinical Study Design

- ✓ **Lateral diffusion between adjacent application sites is negligible.**
- ✓ **Skin re-absorption from systemic compartment is negligible.**

Pilot Study:



No topical application on central application site

Condition	Drug	N	AUC [(ng·h)/mL]
			Geometric Mean
Lidocaine/Prilocaine 2.5% Cream (10 mg/cm²)	lidocaine	23	4,556.91
No topical application (leg)		12	15.77
No topical application (arm)		12	6.65
Lidocaine/Prilocaine 2.5% Cream (10 mg/cm²)	prilocaine	23	8,603.01
No topical application (leg)		12	28.05
No topical application (arm)		12	7.09

Results from clinical dOFM verification pilot study

Even in a worst case scenario (60 g cream applied) only ~0.5% AUC of the treated site were found in untreated skin (arm).

- lidocaine: 0.48% of treated AUC
- prilocaine: 0.52% of treated AUC

Results from clinical dOFM verification main study – high dose

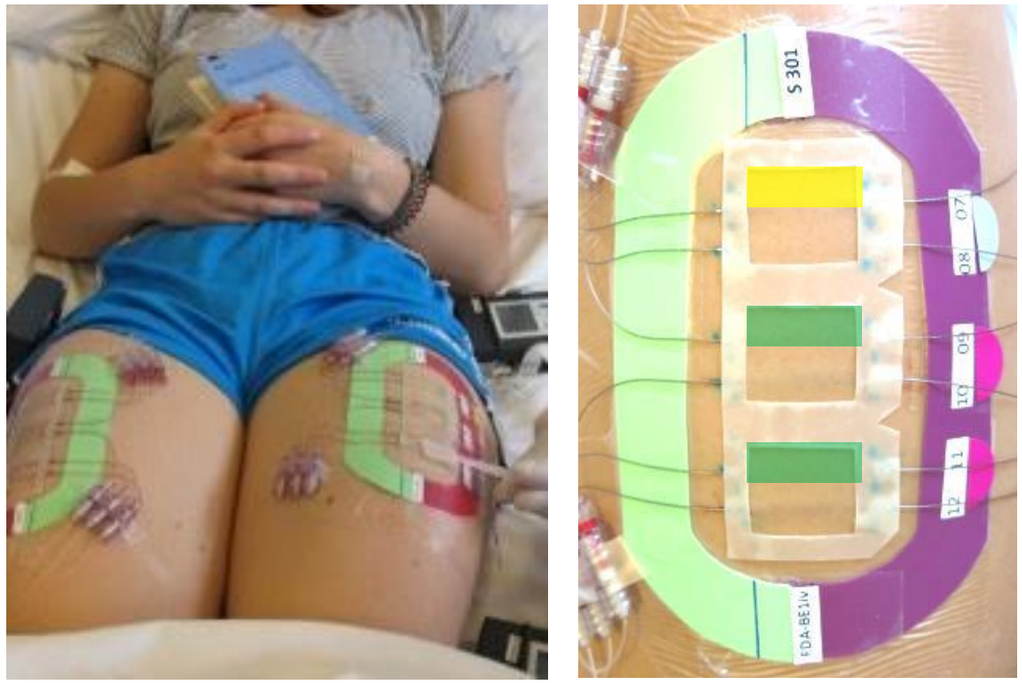
Suitability of dOFM for different classes of topical drugs

dOFM pivotal BE verification study

➔ ***low hydrophilic and low protein-bound API***

- 20 healthy subjects
- Reference Listed Drug (R): Zovirax® US
- Test Product (T): Aciclovir-1A Pharma Austria
- 36 hours dOFM sampling time
- 12 dOFM probes per subject
- BE calculated by using ABE

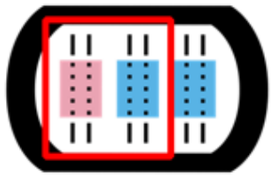
Clinical study outline - acyclovir

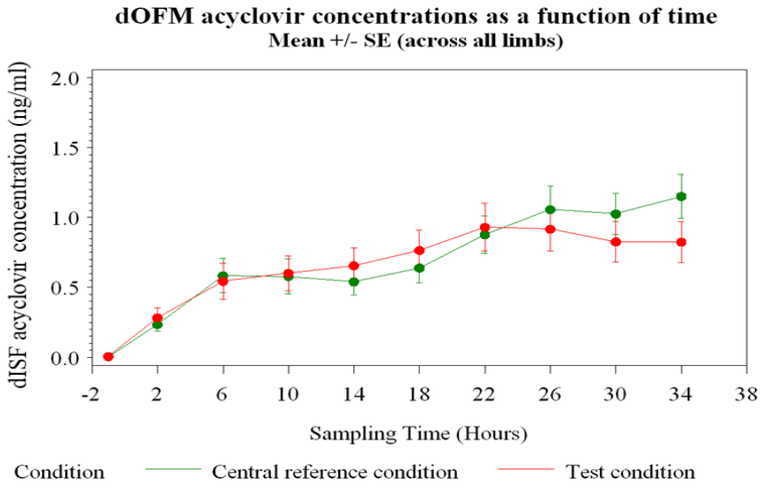


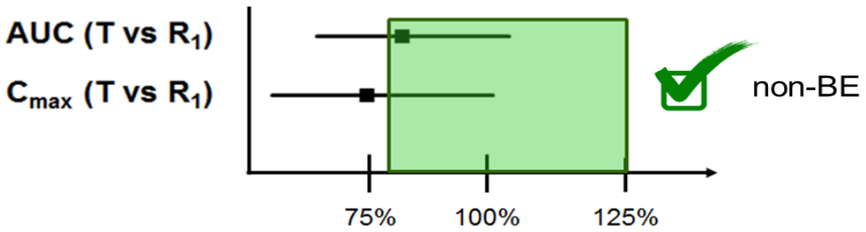
Clinical design of dOFM pivotal BE verification study for acyclovir

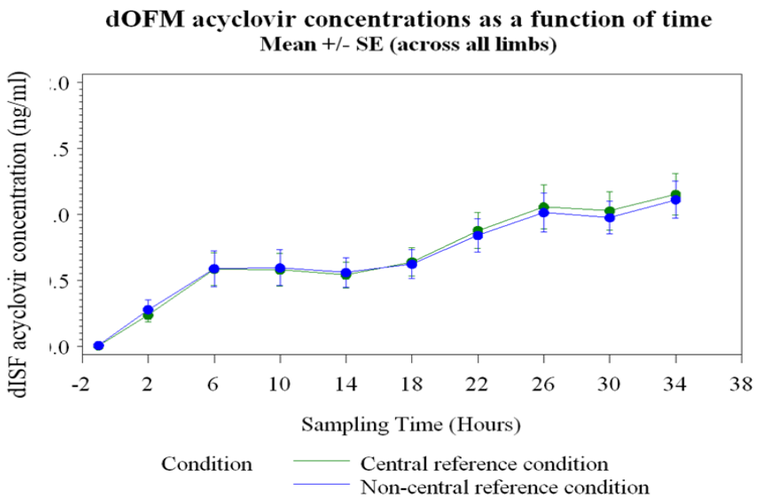
Suitability of dOFM for different classes of topical drugs

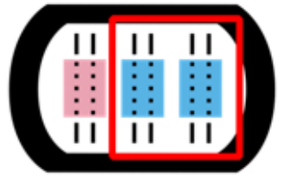
- ✓ dOFM BE verification study failed to show BE for Aciclovir to Zovirax US.
- ✓ dOFM BE verification study showed BE for Zovirax US to itself.

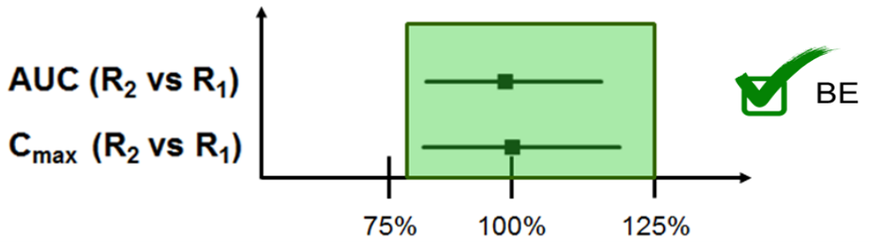












"Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence" Bodenlenz et al. Clin. Pharmacokinet. 2017 doi:10.1007/s40262-016-0442-z.– OPEN ACCESS

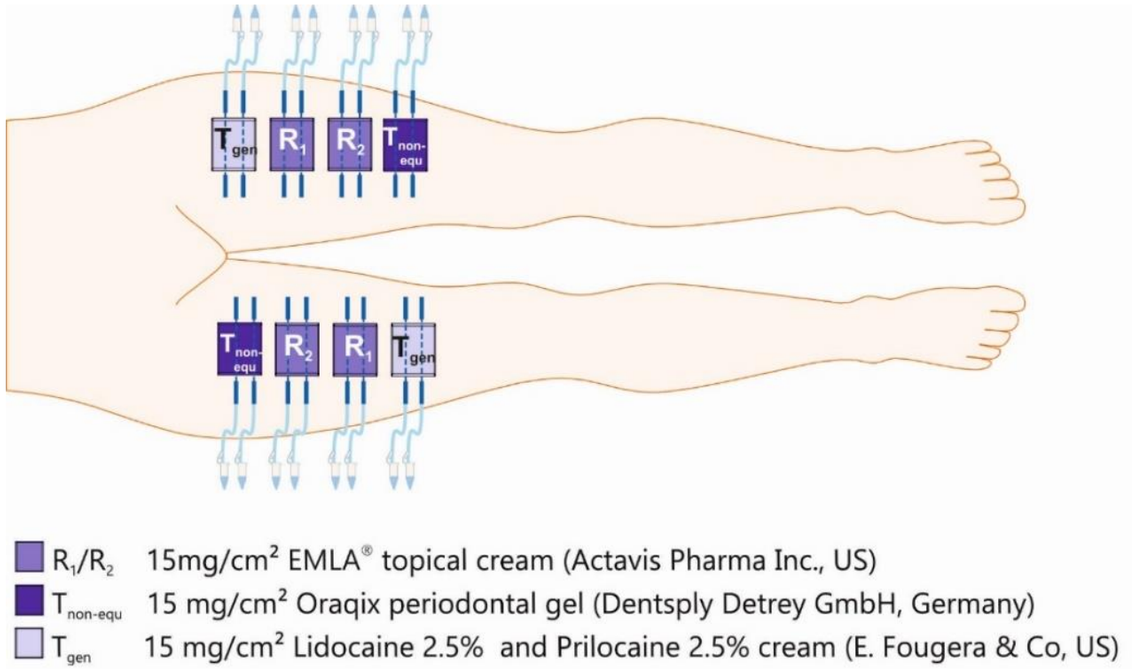
Suitability of dOFM for different classes of topical drugs

dOFM pivotal BE verification study

➔ ***medium hydrophilic and medium protein-bound API***

- 20 healthy subjects
- Reference Drug (R): EMLA® cream
- US-FDA Approved Generic (T_{gen}): Fougera® cream
- Test Product ($T_{non\text{-}eqv.}$): Oraquix ® gel
- Drug dosing for 3 hours
- 24 hours dOFM sampling time
- 16 dOFM probes per subject
- BE calculated by using SABE

Clinical study outline - lidocaine/prilocaine low dose

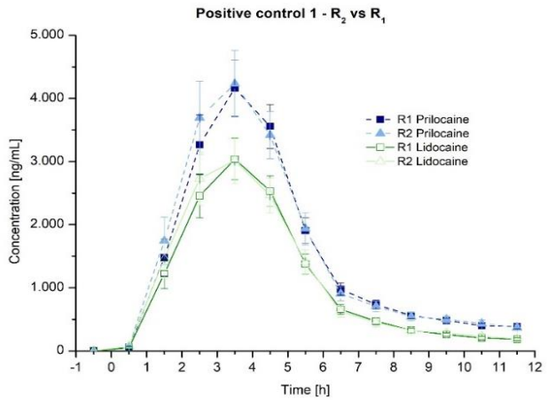


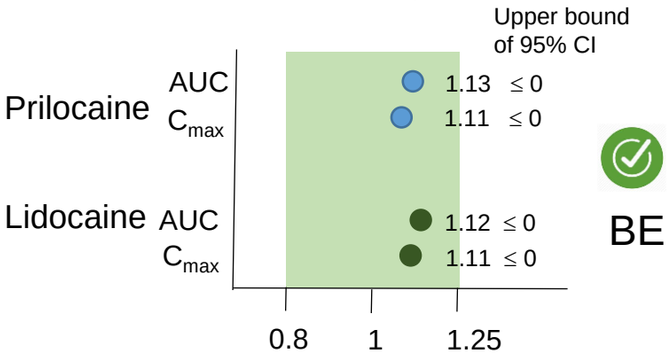
Clinical design of dOFM pivotal BE verification study for lidocaine/prilocaine low dose

Suitability of dOFM for different classes of topical drugs

✓ **dOFM BE verification study showed BE for EMLA to itself.**

EMLA vs. itself (R)



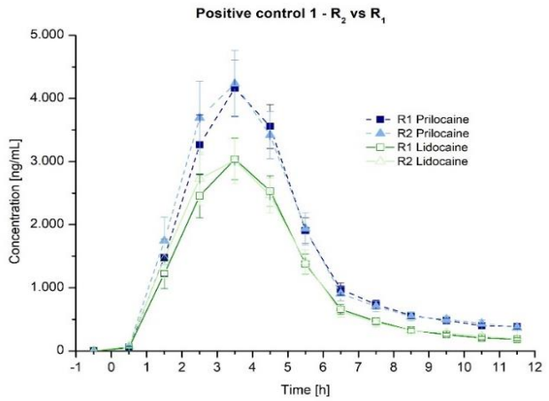


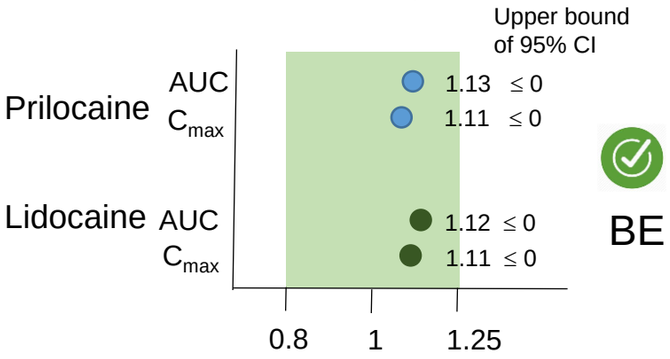
A Clinical Study to Assess the Bioequivalence of Lidocaine and Prilocaine Topical Drug Products Using Dermal Open Flow Microperfusion. Tiffner et al. 2020. Poster @ AAPS PharmaSci3060 Meeting

Suitability of dOFM for different classes of topical drugs

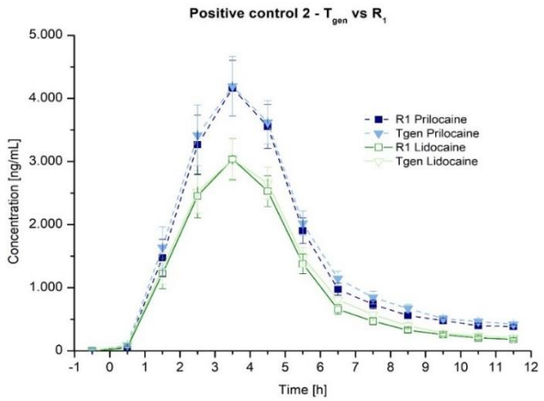
✓ **dOFM BE verification study showed BE for US-FDA approved generic to EMLA.**

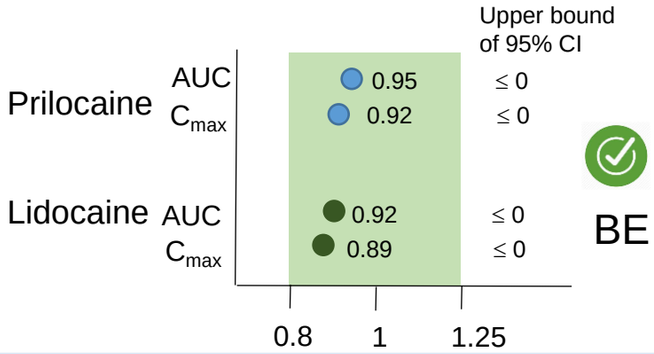
EMLA vs. itself (R)





US-FDA approved generic vs. R (EMLA)





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Suitability of dOFM for different classes of topical drugs

✓ **dOFM BE verification study failed to show BE for Non-BE product to EMLA.**

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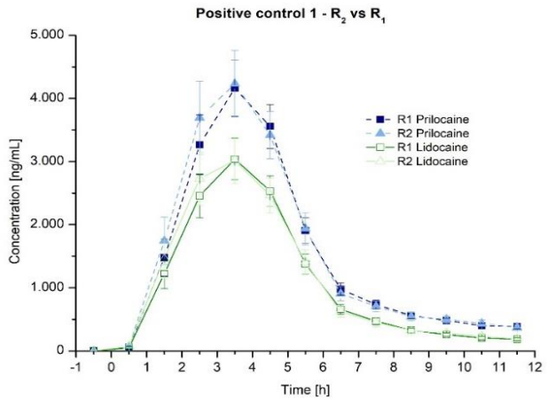
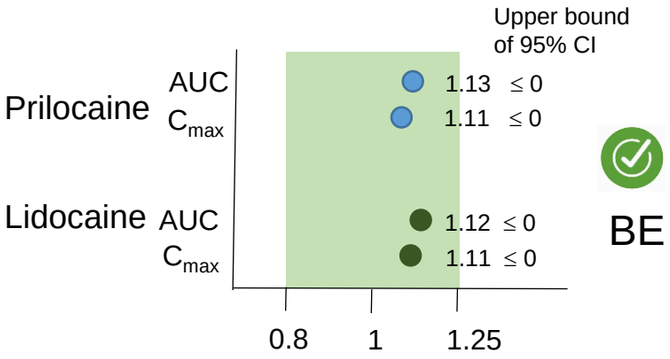
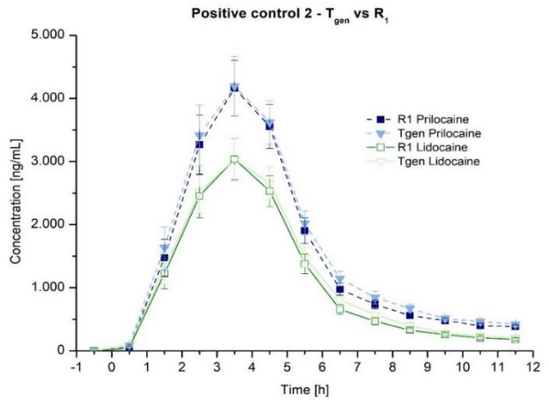
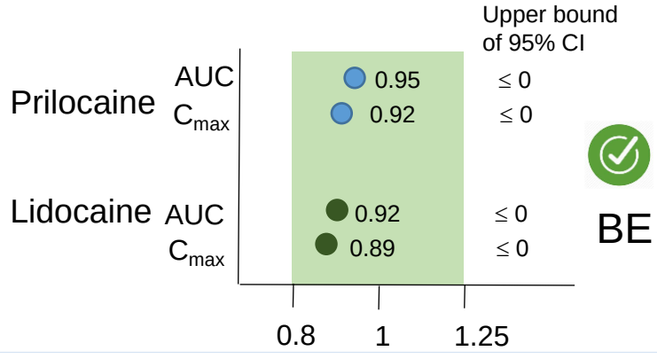




BE

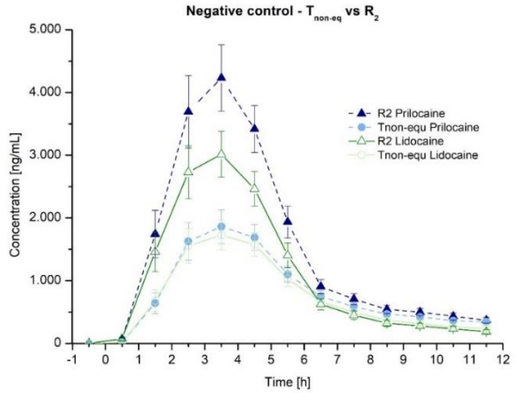
US-FDA approved generic vs. R (EMLA)

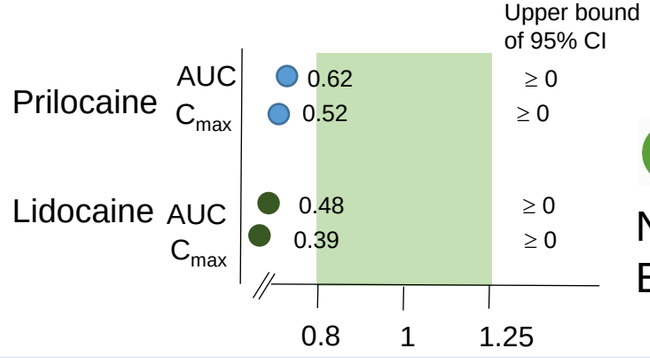




BE

Non-BE drug vs. EMLA





Non-BE

A Clinical Study to Assess the Bioequivalence of Lidocaine and Prilocaine Topical Drug Products Using Dermal Open Flow Microperfusion. Tiffner et al. 2020. Poster @ AAPS PharmaSci3060 Meeting

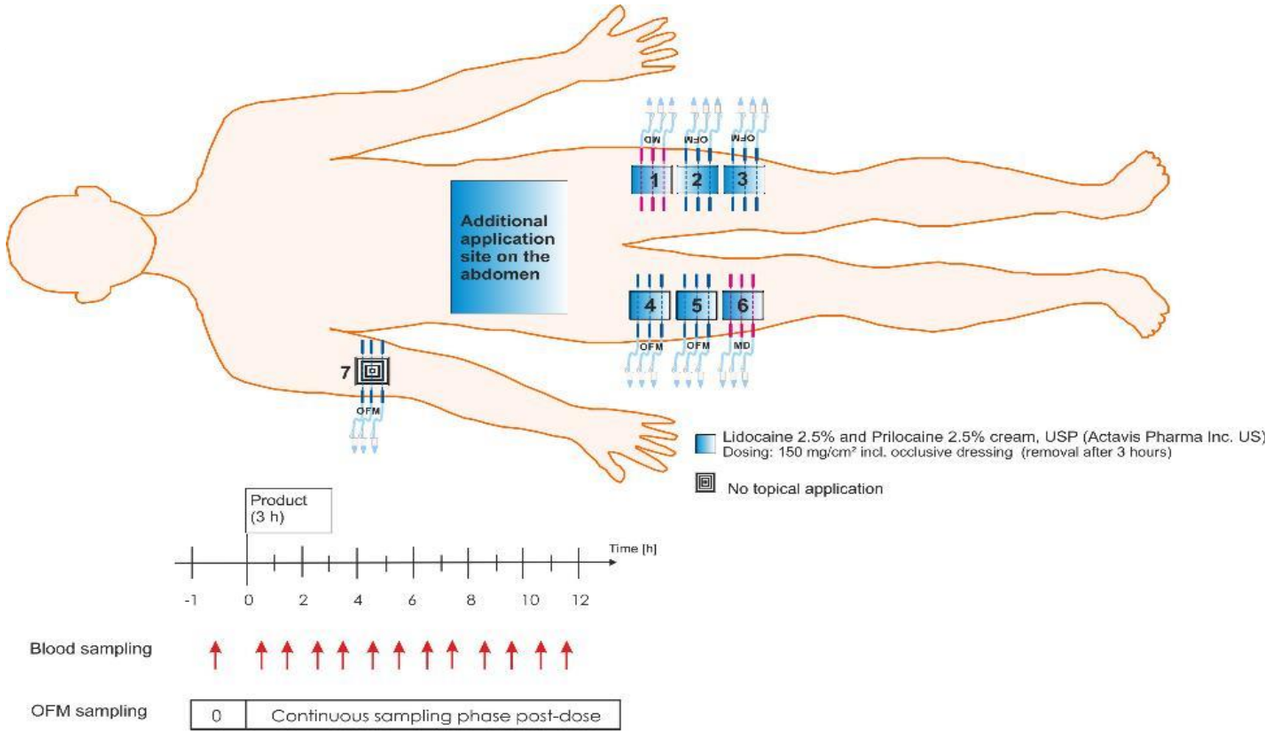
Suitability of dOFM for different classes of topical drugs

dOFM pivotal BE verification study

➔ ***medium hydrophilic and medium protein-bound***

- 20 healthy subjects
- Reference Drug (R): EMLA® cream
- Drug dosing for 3 hours
- 12 hours dOFM sampling time
- 15 dOFM and 6 dMD probes per subject
- BE calculated by using SABE

Clinical study outline – lidocaine/prilocaine high dose

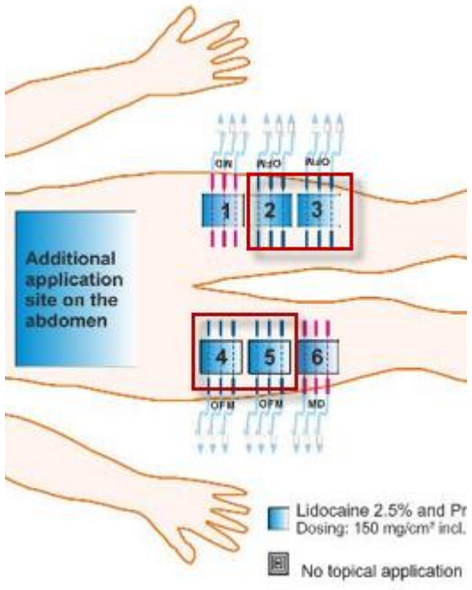


Clinical design of dOFM pivotal BE verification study for lidocaine/prilocaine high dose

Suitability of dOFM for different classes of topical drugs

✓ **dOFM BE verification study showed BE for EMLA to itself at 150 mg/cm².**

Parameter	Analysis variable	Point Estimator (Test/Reference)	Upper bound of the 95% scaled confidence interval	Scaled average BE-criterion satisfied
Lidocaine	LogAUC	1.20	-0.0440	Yes
Prilocaine	LogAUC	1.18	-0.0476	Yes
Lidocaine	LogCmax	1.15	-0.0498	Yes
Prilocaine	LogCmax	1.15	-0.0593	Yes



dOFM pivotal BE verification study for lidocaine/prilocaine high dose

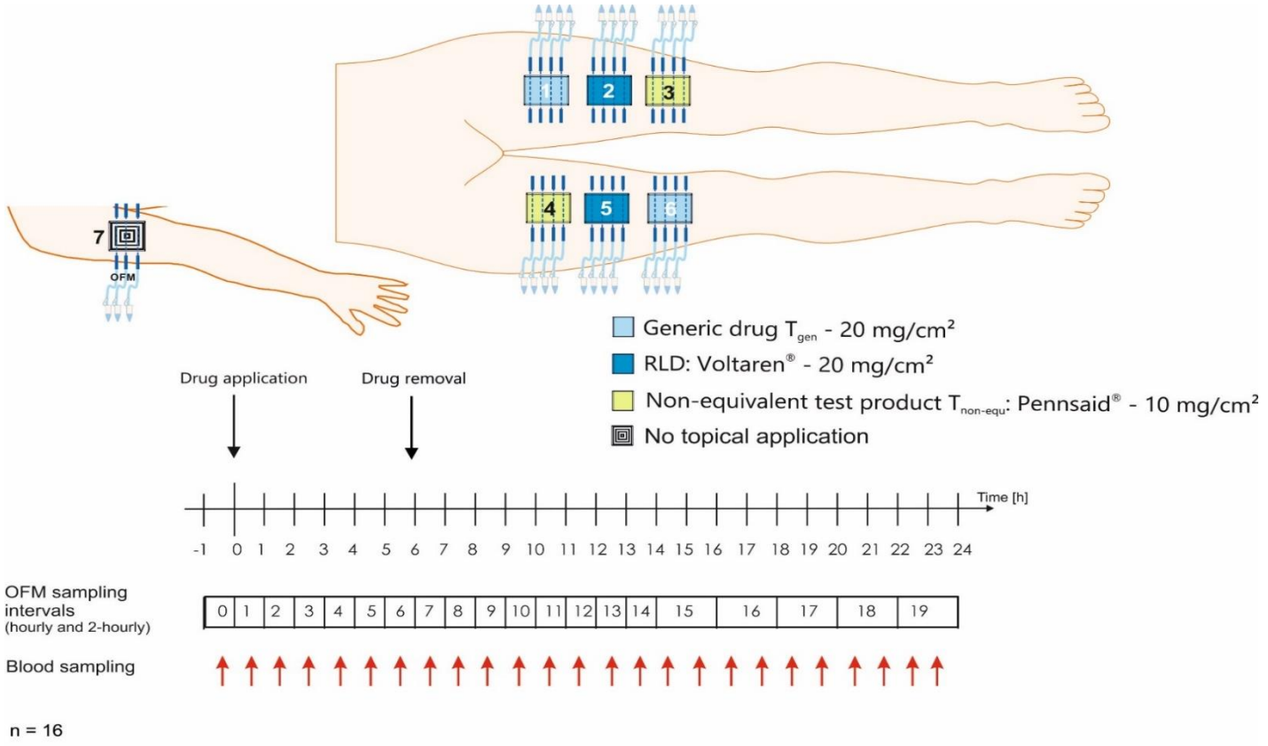
Suitability of dOFM for different classes of topical drugs

dOFM pivotal BE verification study

➔ ***highly hydrophilic and highly protein-bound API***

- 16 healthy subjects
- RLD (R): Voltaren®
- T equivalent : Diclofenac sodium gel 1% (Perrigo)
  US-FDA approved generic
- Tnon-equivalent: Pennsaid® (neg. control)
- Drug dosing for 6 hours
- 24 hours dOFM sampling
- 27 dOFM probes per subject

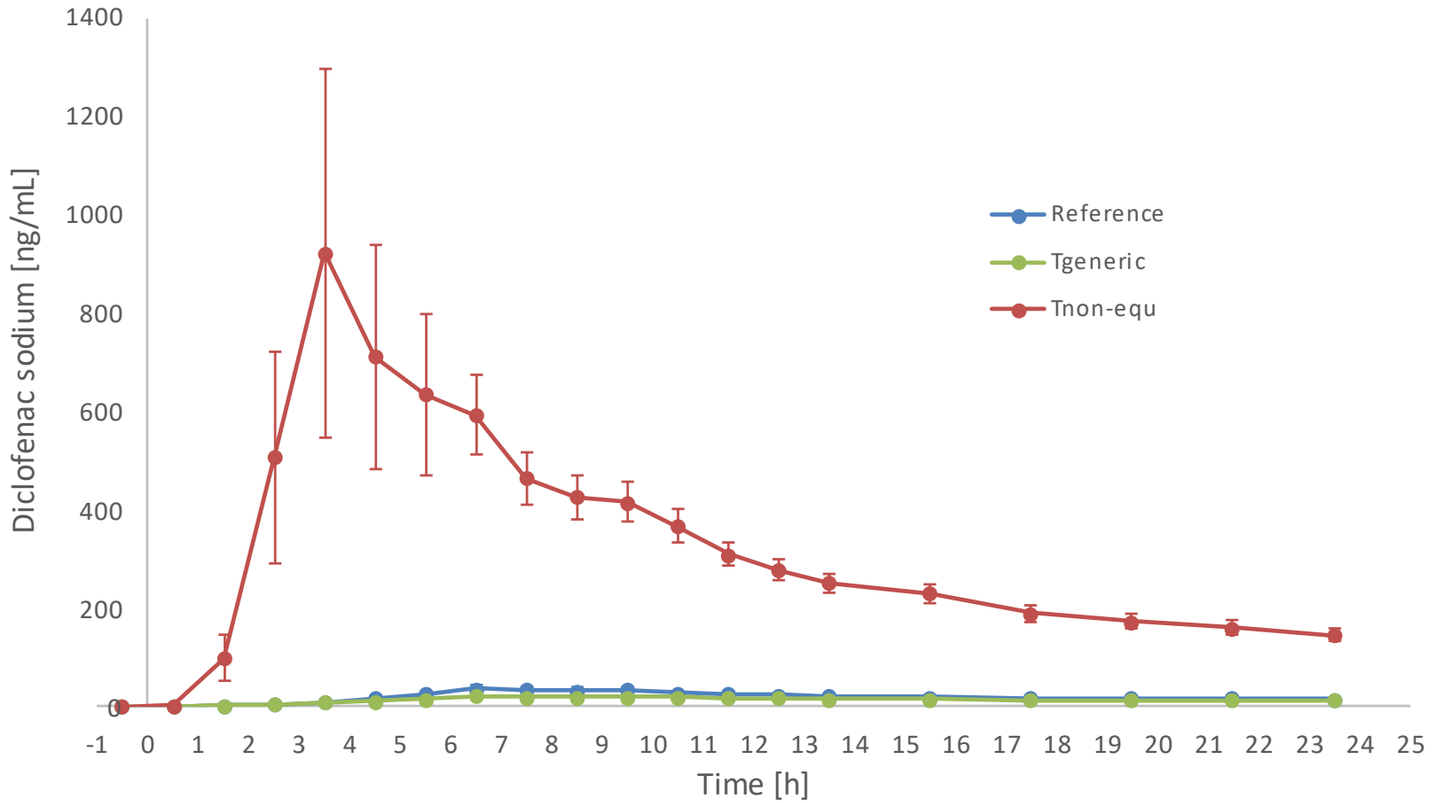
Clinical study outline - diclofenac



Clinical design of dOFM pivotal BE verification study for diclofenac

Suitability of dOFM for different classes of topical drugs

- ✓ **dOFM BE verification study showed different bioavailability of Voltaren® and Pennsaid®.**
- ✓ **dOFM BE verification study showed similarity of US-FDA approved product to Voltaren ®.**



Skin-PK of dOFM pivotal BE verification study for diclofenac

Suitability of dOFM for different classes of topical drugs

- ✓ dOFM BE verification study failed to show BE for non-BE product Voltaren ®.
- ✓ dOFM BE verification study showed BE of US-FDA approved product to Voltaren ® in male subgroup.
- ✓ Data analysis still ongoing

Comparison	Variable	Sex	Point Estimator (Test/Reference)	Within-reference standard deviation	Upper bound of CI95% (SABE) for point estimate	SABE-criterion satisfied
$T_{non\text{-}equ}$ versus R	LogAUC	male	20.49	0.91	10.37	N
$T_{non\text{-}equ}$ versus R	LogAUC	female	14.59	1.26	8.81	N
$T_{non\text{-}equ}$ versus R	$LogC_{MAX}$	male	30.57	0.93	13.67	N
$T_{non\text{-}equ}$ versus R	$LogC_{MAX}$	female	16.12	1.37	9.18	N
$T_{generic}$ versus R	LogAUC	male	0.84	0.94	-0.43	Y
$T_{generic}$ versus R	$LogC_{MAX}$	male	0.80	0.98	-0.41	Y

Requirements of skin PK-based BE Methods

- ✓ **Determine cutaneous PK of a topically applied drug at or near the site of action in the dermis**
- ✓ **Reproducibility and accuracy of PK-based method**
  - ✓ Standardization of equipment and clinical study performance
  - ✓ Reflect changes in skin bioavailability (BA)
- ✓ **Verification of suitability of skin PK-based clinical study design**
  - ✓ General set-up: application of dose, specific dose duration and sampling duration, assessment of absorption and elimination phase (sampling duration of ≥ 12 hours), etc.
  - ✓ Verify sensitivity of skin PK-based method
  - ✓ Absence of lateral cross-talk between application sites and skin re-absorption from systemic compartment
- ✓ **Verification of suitability of dOFM for different classes of topical drugs**
  - ✓ Low hydrophobic and low protein-bound: acyclovir
  - ✓ Medium hydrophobic and medium protein-bound: lidocaine/prilocaine
  - ✓ Medium hydrophobic and medium protein-bound: diclofenac
- Commercial availability of clinical study performance

Commercial availability of clinical study performance

✓ **Now Open: Call for Partnership with CROs to offer dOFM clinical studies**

We invite qualified institutes and organizations to become certified clinical dOFM™ partner

We will provide a comprehensive technology transfer package:

- Transfer, training and certification of the dOFM™ technology and clinical protocols
- Exclusive purchasing/leasing of the clinical dOFM™ components and hardware
- Right-to-use of the dOFM™ trademark and patents for the associated services
- Technology support and optional consultancy service to facilitate trial
- …

JOANNEUM RESEARCH HEALTH

Invitation for Partnership

Clinical Dermal Open Flow Microperfusion

Please visit: https://www.openflowmicroperfusion.com/call-for-partnership
Email: clinical.partner@joanneum.at

SUMMARY

Dermal continuous sampling techniques like dOFM…

- **have advanced over the last decade dramatically.**
- **have the ability to directly measure the rate and extent to which these locally acting drugs become available from topical products at or near their site(s) of action in the skin.**
- **have shown in multiple clinical studies - performed in cooperation with US-FDA - their ability as skin PK-based methods to accurately assess dermal bioavailability.**
- **have shown adequate sensitivity …**

  to show bioequivalence of a reference to itself and to US-FDA approved generic product.

  to not show bioequivalence of a reference to a non-bioequivalent product.

JOANNEUM RESEARCH HEALTH

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Thank you for your attention

dOFM