Clinical Pharmacokinetic Evaluation of Dermal Bioavailability and Bioequivalence

Or: Please Don't Ignore How Skin PK&PD May Reduce Your Topical Drug Development Risk

AAPS Workshop on Dermatological Drug Products—Developmental and Regulatory Considerations

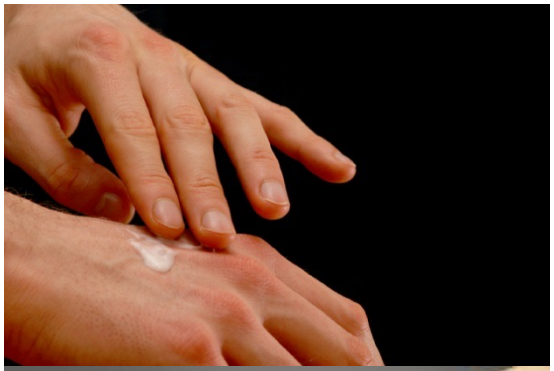
CONTENT
What's coming?

- Tissue Specific PK and PD – Target Tissue Matters!
- Open Flow Microperfusion – An Introduction
- Translational: Link Pre-Clinical to Clinical Results
- NCE: Clinical Proof for Postulated Mode of Action
- Generics: Clinical BE of Topical Acyclovir Products
- Summary

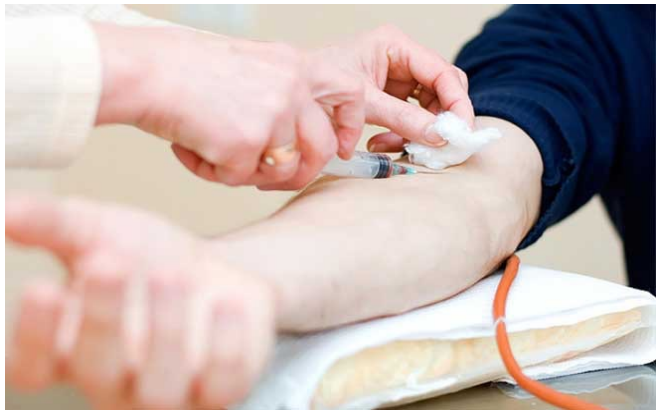
Tissue Specific PK and PD:

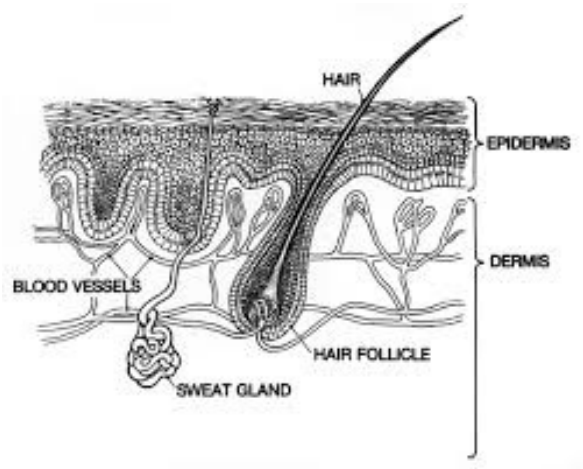
Target Tissue Matters!

The Target Environment Does Matter!



Does blood really reflect your drug‘s PK/PD in the dermis?





The Target Environment Does Matter!

If you want to develop a snow tire and your company is only situated in the Sahara Dessert.

Would you explore the prototype in the dessert?

Or shouldn’t you take the effort to go to Norway in winter time?

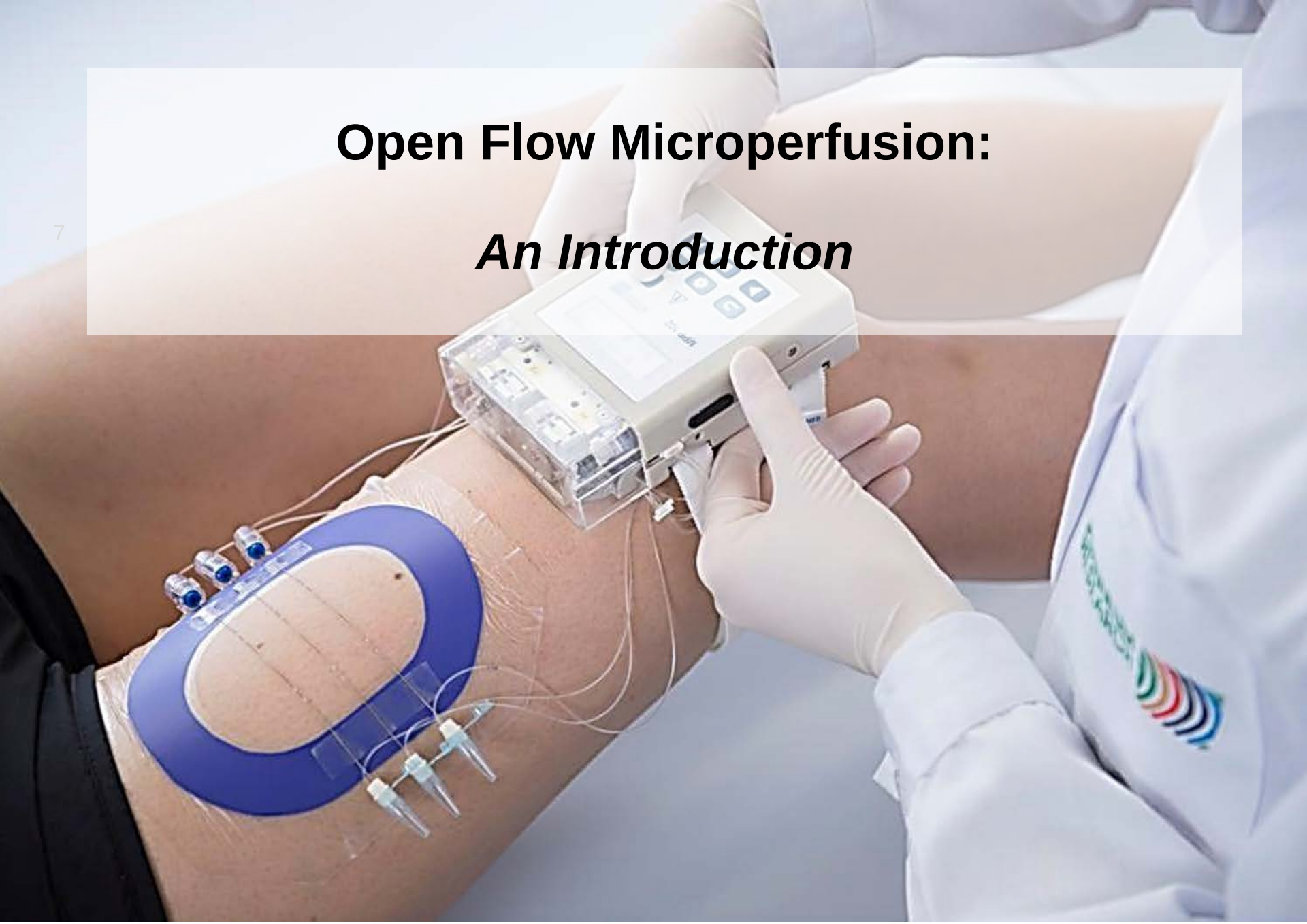
Skin Biopsy

1. Pros
    I. Easy procedure
    II. Allows approximation of drug concentration
    III. Allows approximation of drug effect

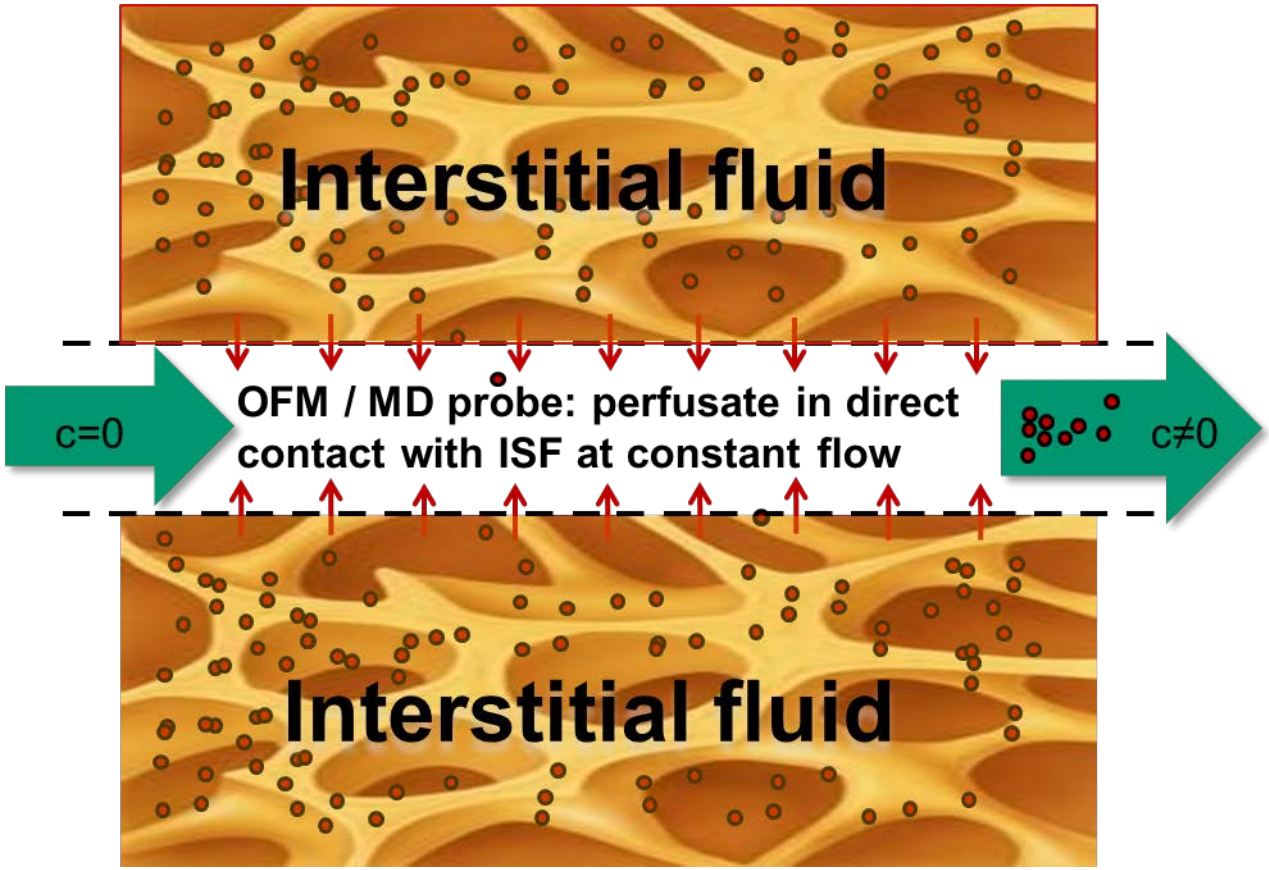
2. Cons
    I. Only sum of intra- and intercellular drug concentration accessible
    II. No PK profile: only one time point per biopsy
    III. Risk of cross-contamination
    IV. Metabolism may not reflect in vivo situation
    V. Insufficient time resolution for real PK in clinical setting

Open Flow Microperfusion:

An Introduction

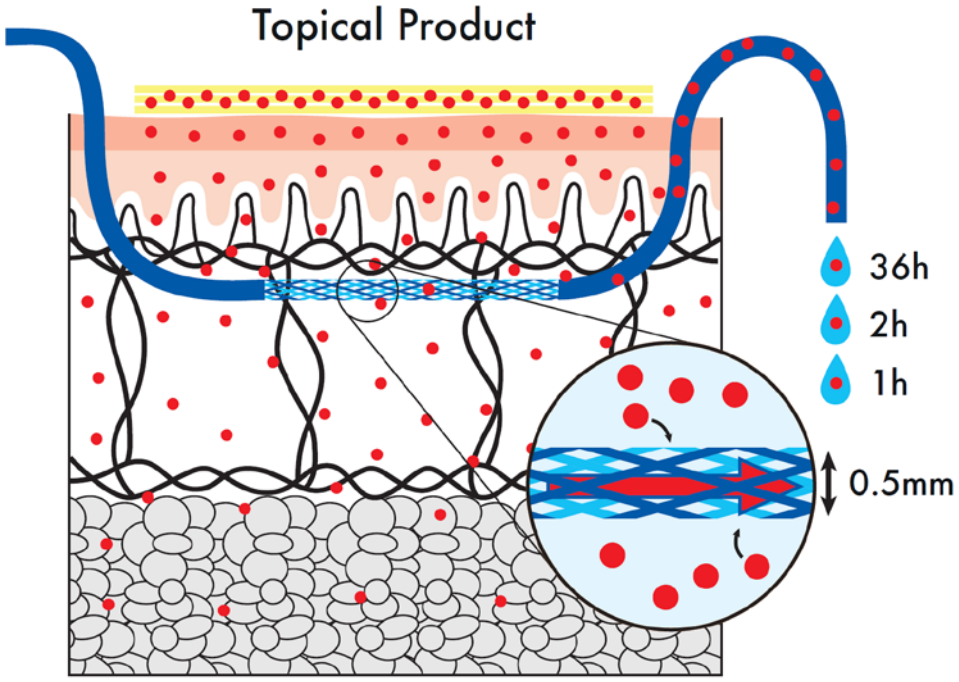


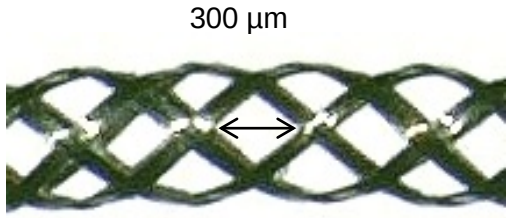
Continuous dermal sampling
working principle



Open Flow Microperfusion
an introduction

✓ **OFM samples represent diluted but unfiltered interstitial fluid**

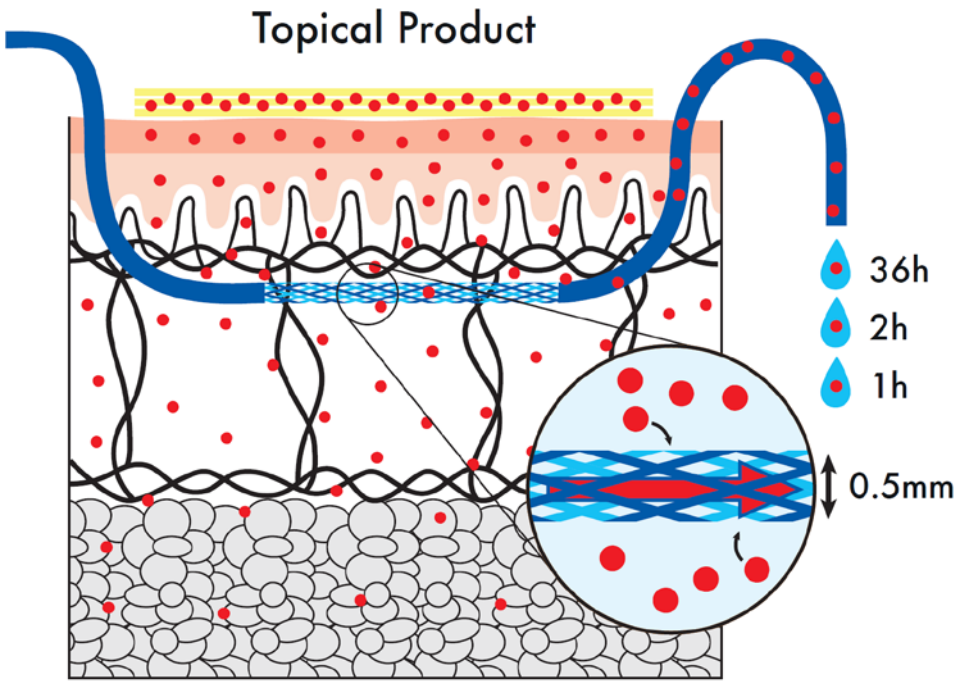




CE-certified for clinical use

Open Flow Microperfusion

✓ **All drugs are accessible in-vivo in the dermis**



lipophilic substances

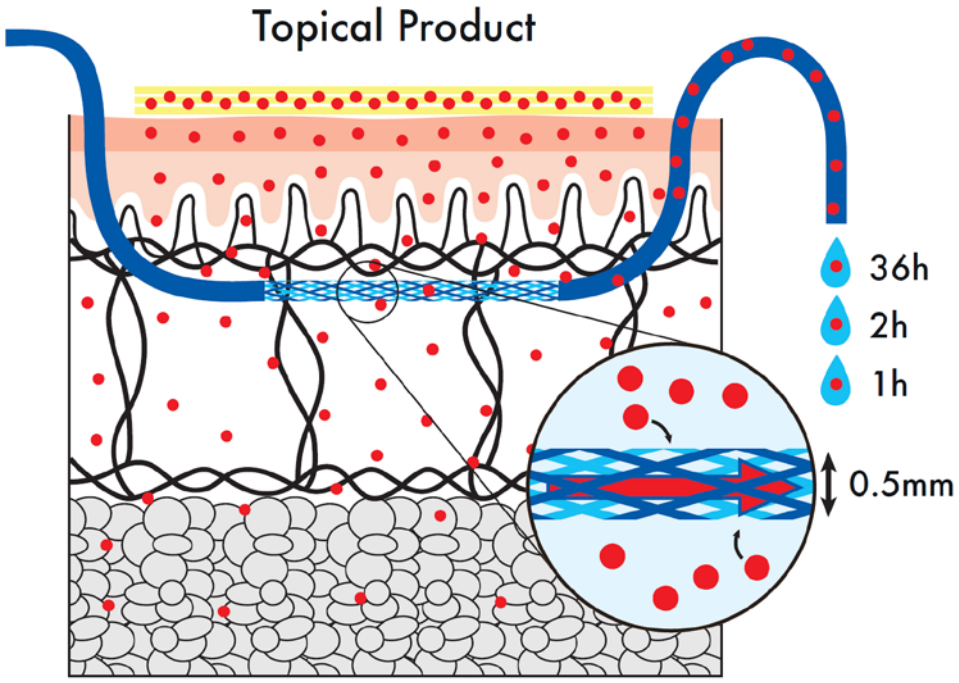
Bodenlenz et al. 2016 (CP-17; logP 3.5)
Holmgaard et al. 2011 (Fentanyl; logP 4.5)

high molecular weight substances (up to cells)

Dragatin et al. 2016
(Quantification of antibodies in skin)
Kolbinger et al. 2016
(Cytokines in the skin in healthy & patients)

Open Flow Microperfusion

✓ **dOFM shows dose dependent dermal AUC profiles**

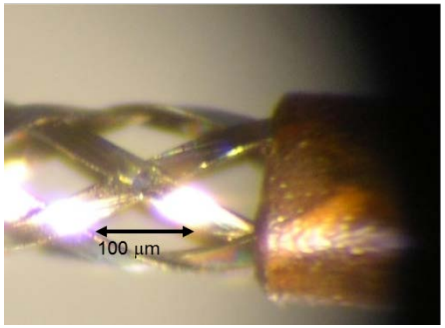


Clinical dOFM studies in skin:

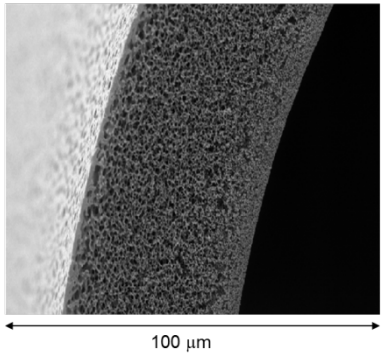
Corticoid (topical) – 26 h clinical
Antibody (SC) – 17 h clinical
Acyclovir (topical) – 36 h clinical

OFM and MD
application range

OFM: 100 µm open exchange areas



MD: membrane, nm-µm pores



Substance / Drugs …	MD	OFM
… small	YES	YES
… hydrophilic(small)	YES	YES
… larger + large	YES & NO	YES
… lipophilic (super lipophilic)	NO	YES
… protein-bound	NO	YES
… (nano)carrier / cells	NO	YES

MD: PK/PD of small and hydrophilic substances
OFM: PK/PD of ANY substance independent of size and lipophilicity

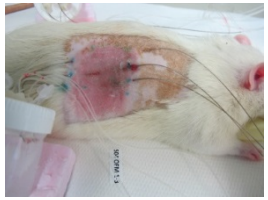
Translational:

Link Pre-Clinical to Clinical Results

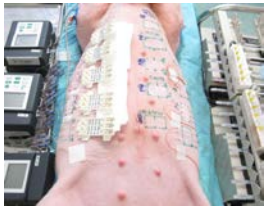
Link pre-clinical to clinical results
Identical method – different models

IN-VIVO

rat



pig



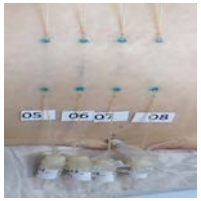
healthy volunteer

patient

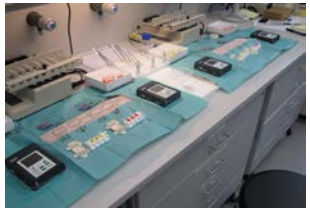
EX-VIVO

pig
(freshly excised)

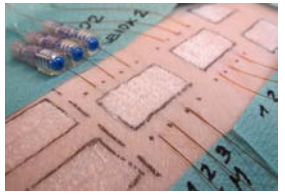
pig
(frozen)



healthy human
(frozen)

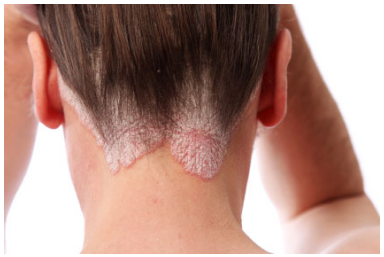


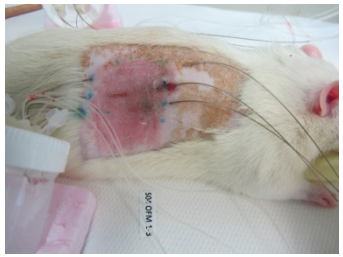
healthy human
(freshly excised)

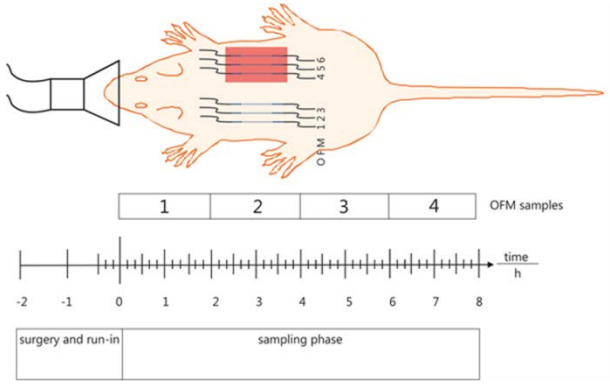


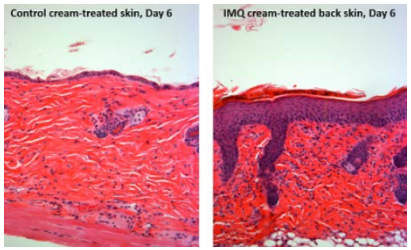
Preclinical Proof of Concept
mode of action of your API in-vivo

Case Study (Sanofi Genzyme)[2]









Dermal API PK for dose-response ← HPLC-MS/MS

Dermal PD on cytokine level ← OLINK

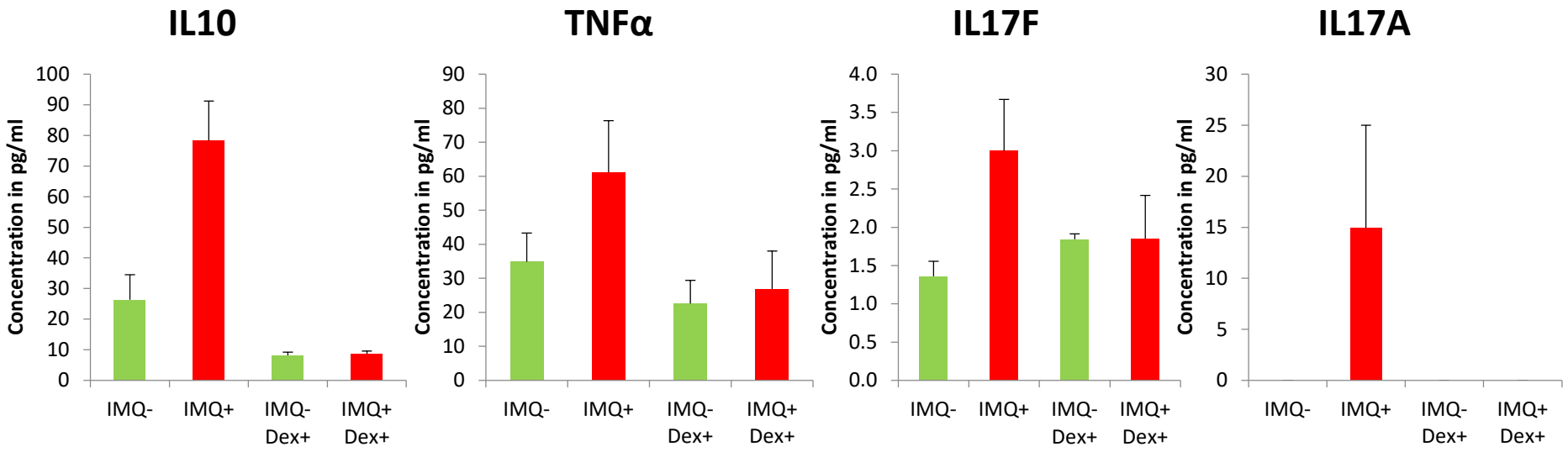
Dermal PD on immune cell level ← FACS

in-vivo effect of API on cytokine and immune cell level

[2] unpublished results: from Genzyme: Thomas Hultsch, Kyriakos Economides, Arun.Subramaniam

Preclinical Proof of Concept
mode of action of your API in-vivo

Case Study (Sanofi Genzyme)[2]

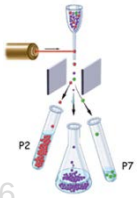


Data are mean ± SE, n=6; 8 days of treatment

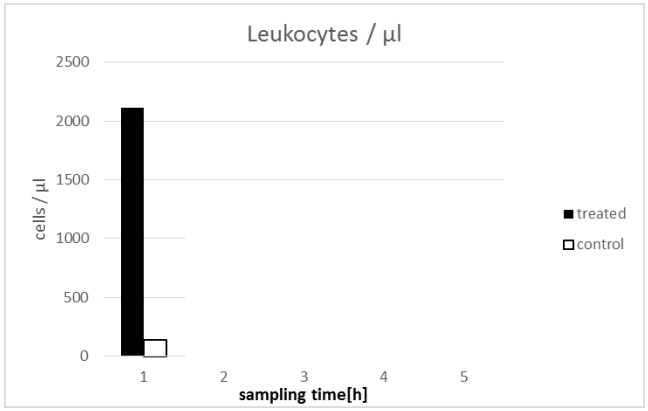
IMQ: Imiquimod; DEX: Dexamethasone

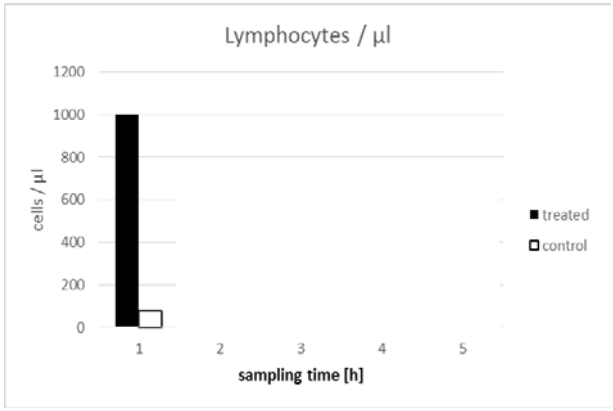
IMQ-Rat Model is an in-vivo model for psoriatic inflammation

[2] unpublished results: from Genzyme: Thomas Hultsch, Kyriakos Economides, Arun.Subramaniam



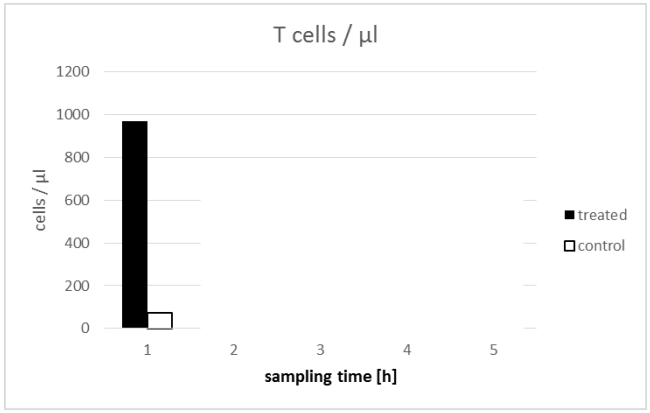
Preclinical Proof of Concept
mode of action of your API in-vivo

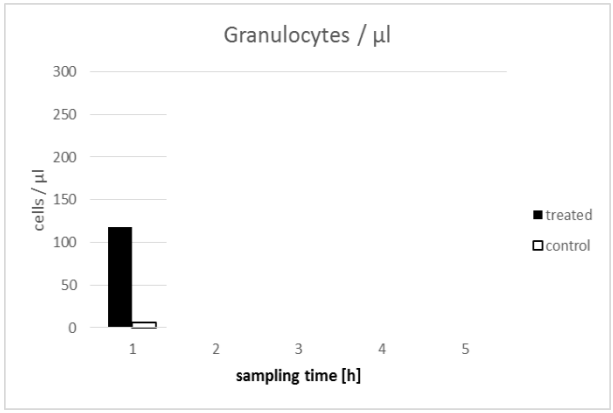


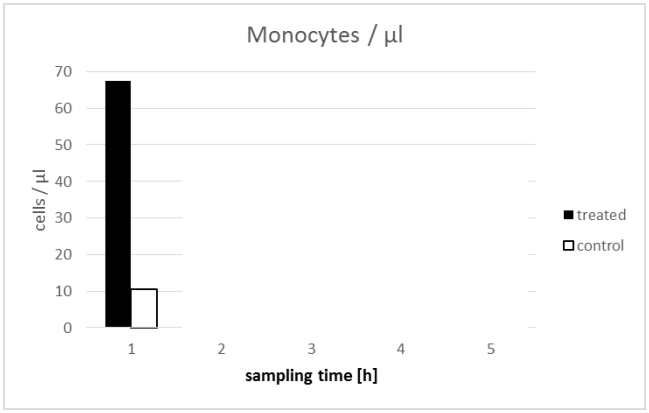


lesional

control







This psoriasis animal model allows PK and PD investigations

unpublished results

New Chemical Entity:

Clinical Proof of Mode of Action

OFM

PK/PD of an Antibody Drug: Case Study Secukinumab

Background and Objectives

- Secukinumab, a fully human monoclonal antibody that selectively targets IL-17A, has demonstrated efficacy in phase 3 trials, within 16 weeks of initiation of treatment.
- The objective of this exploratory, single-center, open-label study (NCT01539213) was to further characterize the mechanism of action of secukinumab in the skin in
  - 8 healthy volunteers (Part 1)
  - 8 plaque psoriasis patients (Part 2)
- OFM was performed on Day 1, 8 and 15 in Part 1 and 2

OFM

PK/PD of an Antibody-Drug: Case Study Secukinumab

Primary Aim

- Absolute quantification of secukinumab in the dermis of healthy volunteers and psoriatic patients.

Secondary Aims

- Investigate if postulated signaling pathways are different in healthy and psoriatic patients in dermis ⇨ IL17a pathway.
- Investigate postulated mode of action ⇨ down stream IL17a marker.
- Investigate drug effect on a protein level ⇨ mediator for keratinocyte proliferation and angiogenesis and keratinocyte mobility.

OFM

PK of an Antibody-Drug: Case Study Secukinumab

Primary Aim: Absolute quantification of secukinumab in the dermis of healthy volunteers and psoriasis patients

Serum and Dermal Secukinumab Levels (µg/mL, mean ± SD)					
Healthy Volunteers (n = 8)					
Serum		Dermal ISF[a,b]		Skin biopsy[c]	Blister fluid
Day 8	Day 15	Day 8	Day 15	Day 15	Day 15
36.1 ± 10.5	35.0 ± 10.5	7.76 ± 1.30	8.02 ± 3.23	10.40 ± 3.97	6.89 ± 2.26

- **Dermal ISF concentrations ~22% of serum**
- **Dermal concentration by OFM, blister fluid, biopsies are comparable.**

OFM

PK of an Antibody-Drug: Case Study Secukinumab

Primary Aim: Absolute quantification of Secukinumab in dermis in healthy volunteers and psoriatic patients

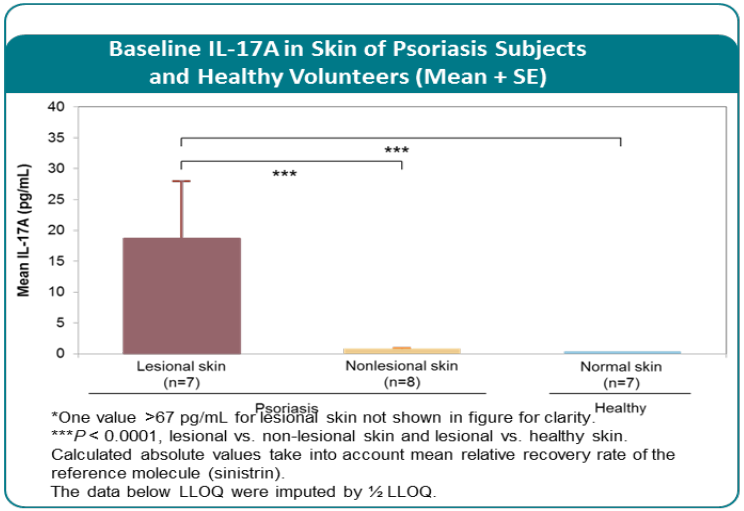
Serum and Dermal Secukinumab Levels (µg/mL, mean ± SD)					
Psoriatic Subjects (n = 8)					
Serum		Dermal ISF[a,b]			
Day 8	Day 15	Day 8		Day 15	
		L	NL	L	NL
21.1 ± 4.3	21.2 ± 4.9	6.76 ± 2.68	8.34 ± 3.35	5.65 ± 1.80	6.39 ± 3.35

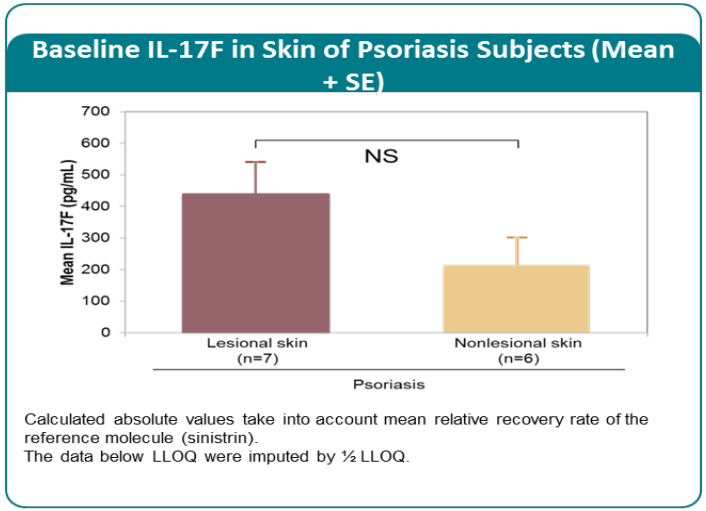
- **Dermal ISF concentrations are 28-39% of serum concentration.**
- **Dermal ISF concentrations on day 8 and day 15 are similar.**

OFM

PD of an Antibody-Drug: Case Study Secukinumab

Secondary Aim: Investigate that postulated signaling pathways are different in healthy volunteers and psoriatic patients in dermis - IL17a pathway



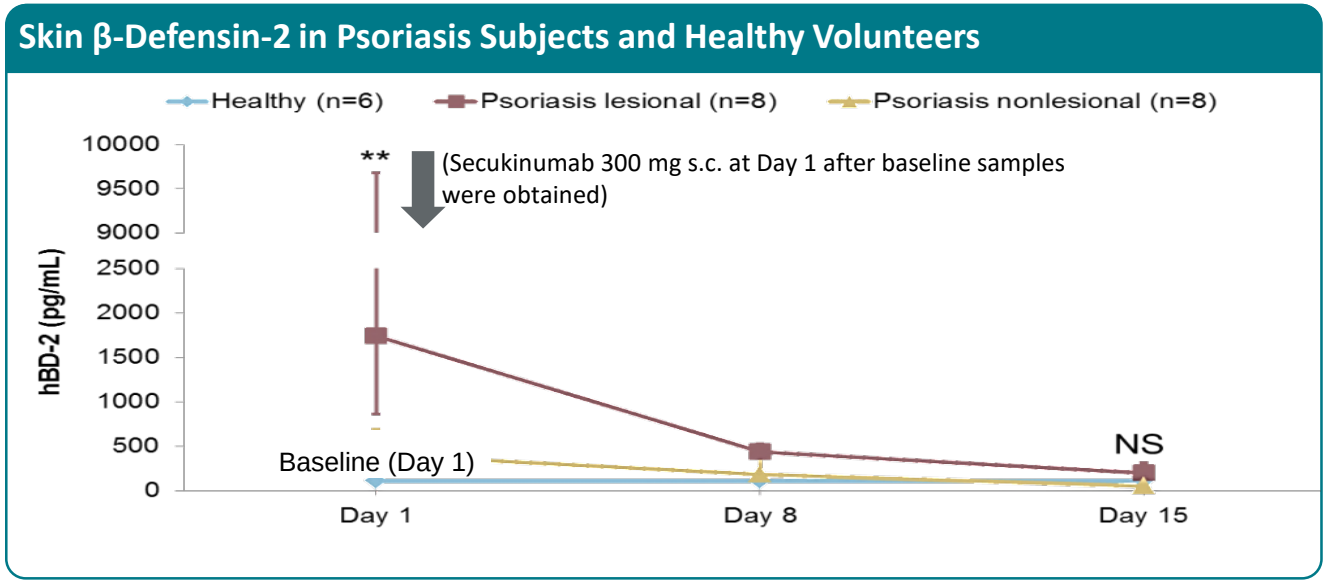


IL-17A, but not IL-17F, is significantly higher in psoriatic lesional skin compared with non-lesional skin or skin of healthy volunteers.

OFM

PD of an Antibody-Drug: Case Study Secukinumab

Secondary aim: Investigate postulated mode of action - downstream IL17a marker



ß-defensin-2 protein levels are elevated in psoriatic lesional skin and serum and decrease rapidly in response to secukinumab treatment.

OFM

PK/PD of an Antibody-Drug: Case Study Secukinumab

Conclusions on Pharmakokinetics

- Substantial levels of secukinumab are observed in skin suggesting the potential for local action.
- Secukinumab ISF distribution into psoriasis lesional and non-lesional skin is similar and is higher than ISF distribution in healthy control skin.

Conclusions on Pharmakodynamics

- Key molecular factors and processes implicated in the pathophysiology of psoriasis were positively impacted in psoriatic skin within 7 days of treatment.
- Secukinumab concentration in skin is sufficient to neutralize IL-17a in psoriatic skin
- Secukinumab affected the expression of a number of pro-inflammatory cytokine.

In Vivo Dermal Open Flow Microperfusion:

A Novel Approach to Evaluate Topical Bioavailability and Bioequivalence

Funding for this project was made possible, in part, by the Food and Drug Administration through grants 1U01FD004946 and 1U01FD005861. The views expressed in this presentation do not reflect the official policies of the Food and Drug Administration, or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government. The human research study was approved by the FDA Research Involving Human Subject Committee (RIHSC) and the local Institutional Review Board (IRB) of the Medical University Graz, Austria

BA/BE of generic drugs

oral route

Dosage form → Drug in solution → Biological barrier → Blood → Site of activity → Therapeutic effect

BA/BE

end point study

Dosage form → Drug in skin → Site of action → Therapeutic effect → ~~Blood~~

topical route

BA/BE

end point study

Clearence

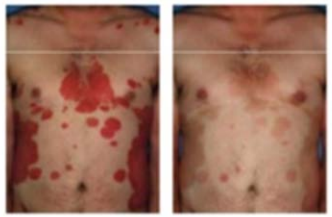
Dermal Open Flow Microperfusion
Vision

FDA approval for topical generic drugs - with some exceptions – requires a

Comparative Clinical Endpoint Bioequivalence Study

Vision: Using dOFM for PK-based Bioequivalence Studies

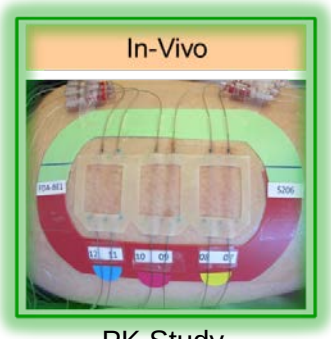
In-Vivo



Endpoint Study

Patients
Hundreds to thousands
Several month to years

In-Vivo



PK Study

Healthy subjects
20 - 40
Few weeks

Skin PK-based BE approaches using dOFM

Strengths

1. Provide a direct in-vivo measurement of the rate and extent of the active moiety at or near the site of action in the skin.
2. Evidence indicates that dermal sampling has the potential to differentiate pharmacokinetic profiles by their magnitude.

Challenges

1. Limitations of existing sampling methods
   → no limitation as dOFM samples diluted ISF
2. Limited sampling time, often < 8 hours
   → no limitation as dOFM samples up to 48 hours
3. High variability of skin PK data
   → optimization of dOFM during the project

Clinical Bioavailability
Overall Approach

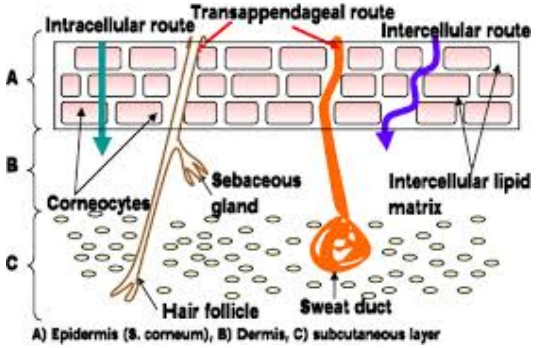
Overall AIM: Investigate the capability of dOFM to address BE and non-BE of topical formulations in-vivo.

- Head-to-head comparison within one subject to minimize inter-subject effect on BE.

- Use application-triplets with
  - two separate application sites for reference product → for BE
  - one application site for a non-Q1 product → for non-BE
- Healthy subjects with intact skin integrity for best discrimination of formulations.
- Use a drug for which skin PK was never successfully monitored in healthy subjects.

dOFM
Controlled or Monitored Parameters

✓ **Controlling all significantly contributing factors which add data variability - or at least monitoring them.**

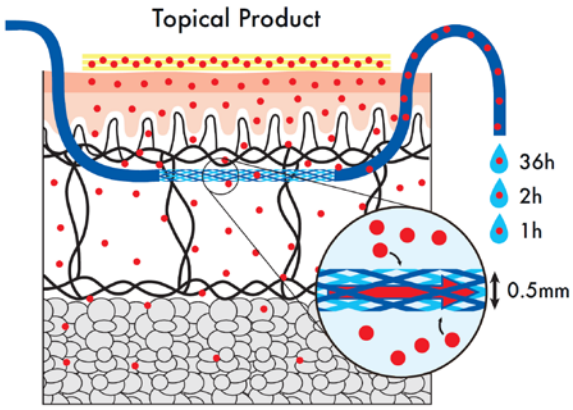


Variations may result from differences in

Hairiness	➔ not controlled
Hair shaving	➔ **subjects are shaved 5 days before dOFM visit**
Sweat duct	➔ not controlled
Skin barrier (stratum corneum) properties	➔ **monitored by TEWL and Impedance**
Skin care products use	➔ **not allowed 5 days before dOFM visit**
Skin condition (e.g. Solarium)	➔ **visual check at screening visit**
Room temperature and humidity	➔ **controlled at 22 ± 1° C ; 40 - 60% rel. humidity**

dOFM
Controlled or Monitored Parameters

✓ **Controlling all significantly contributing factors which add data variability - or at least monitoring them.**



Variations may result from differences in

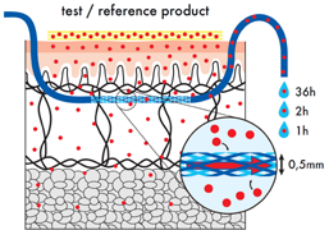
Trauma formation
Application site
Dosage application
Probe depth
Flow rate
Local blood flow
Lateral diffusion and cross-talk
Systemic absorption and cross-talk

Universal Parameters

Drug Dependent Parameters

dOFM
Trauma formation

✓ **Minimized trauma formation by cooling.**



Variations may result from differences in

Trauma formation
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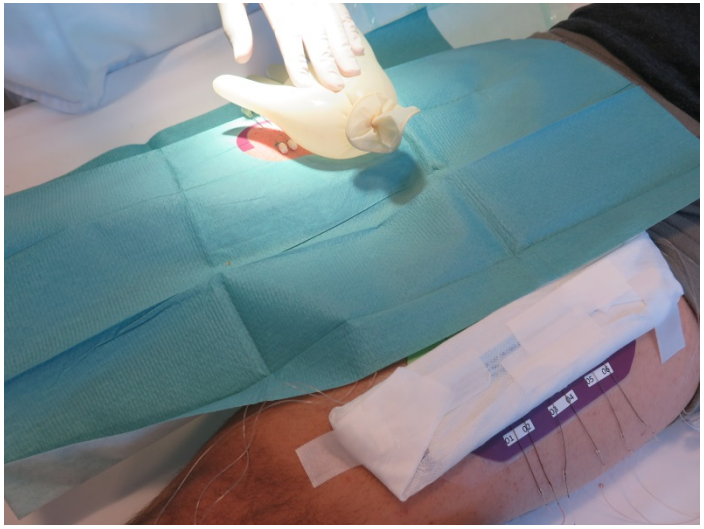
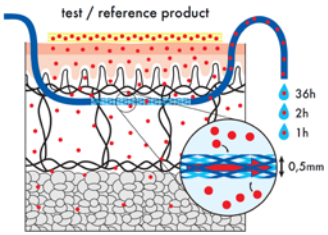
Systemic absorption and cross-talk

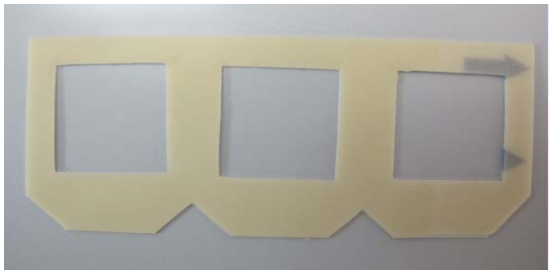


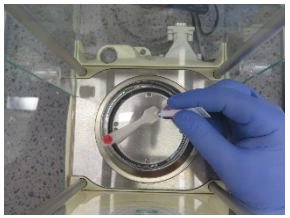
Standardized by cooling after dOFM insertion

dOFM
Drug application

✓ **Homogeneous drug application by using an application template.**







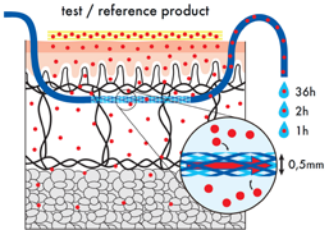
Variations may result from differences in

Trauma formation
Application site
Dosage application
Probe depth
Flow rate
Local blood flow
Lateral diffusion and cross-talk
Systemic absorption and cross-talk

Standardized by use of application template
and
Standardized application (mg/cm²)

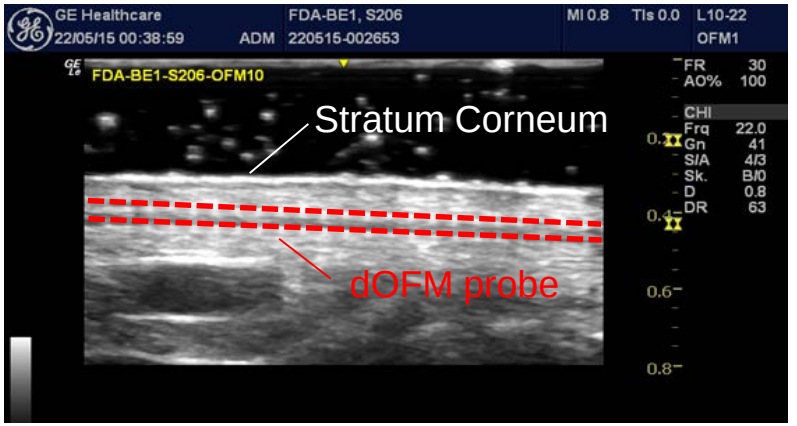
dOFM
Probe depth

✓ **dOFM probe depth measurement for each probe.**



Variations may result from differences in

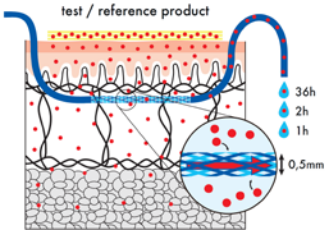
Trauma formation
Application site
Dosage application
Probe depth
Flow rate
Local blood flow
Lateral diffusion and cross-talk
Systemic absorption and cross-talk



Depth of exchange area measured by ultrasound

dOFM
Flow rate

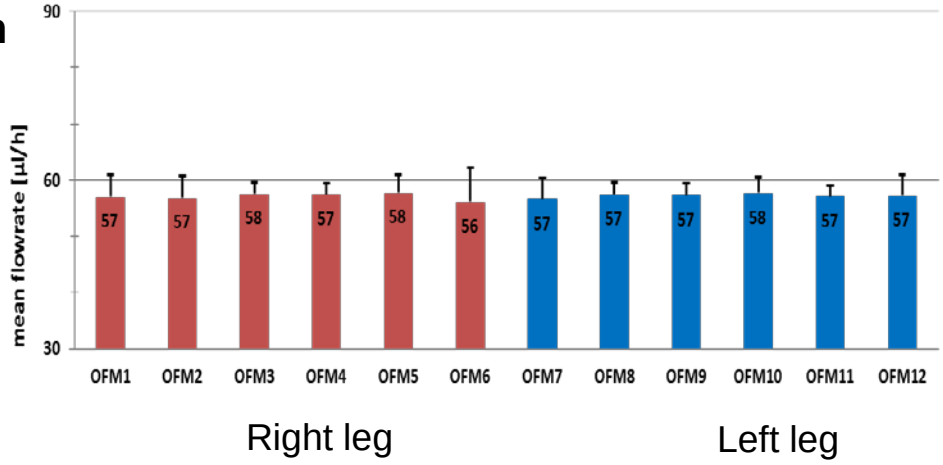
✓ **Stable flow rate of dOFM probes over 36 hours.**



Variations may result from differences in

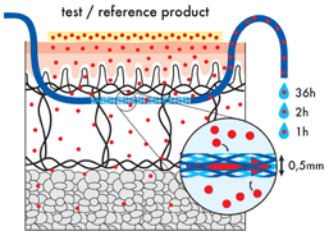
Trauma formation
Application site
Dosage application
Probe depth
Flow rate
Local blood flow
Lateral diffusion and cross-talk
Systemic absorption and cross-talk

Flow rates of all probes in one subject



dOFM
Local blood flow

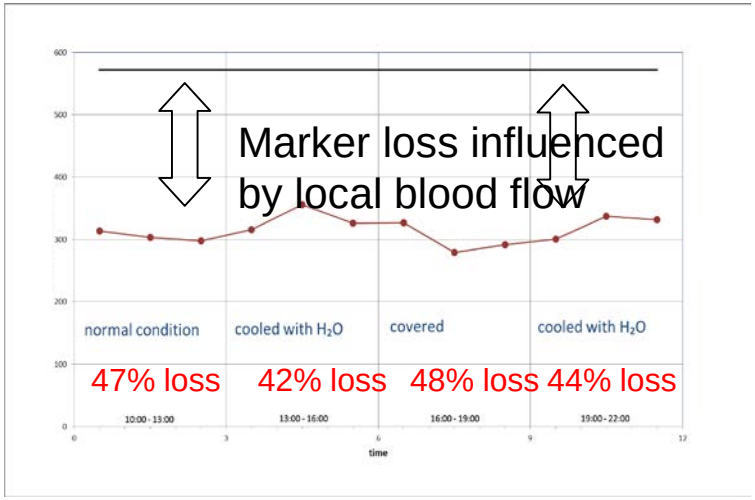
✓ **Monitoring local blood flow by internal standard in OFM perfusate.**



Variations may result from differences in

Trauma formation
Application site
Dosage application
Probe depth
Flow rate
Local blood flow
Lateral diffusion and cross-talk
Systemic absorption and cross-talk

Local blood flow monitoring by loss of glucose from dOFM perfusate

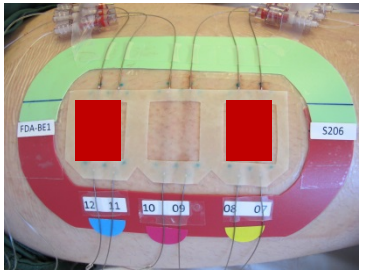


dOFM
Lateral diffusion and cross-talk

✓ **Lateral diffusion for acyclovir is negligible.**

Lateral Diffusion between adjacent application sites

- $R = \frac{|\#dOFM\ Samples\ BLANC\ SITES>LLOD|}{|\#dOFM\ Samples\ US\ ZOVIRAX\ SITES>LLOD|}$
- Definition: no lateral diffusion if $R < 0.05$



US Zovirax
Very high dose
of 50 mg/cm²

Methodology

- results from all 6 subjects of phase 1
- 10,000 bootstrap estimates were computed
- creation of confidence interval for the true population value of the test statistic R
- a one-sided 95% confidence interval was constructed

Results

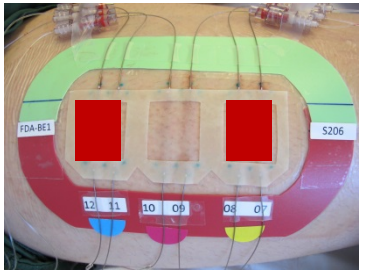
MIN	MEDIAN	P90	P95	P99	MAX
.007633588	0.076336	0.10853	0.11831	0.13492	0.18248

dOFM
Systemic absorption and cross-talk

✓ **No systemic exposure and thus no influence on PK of dOFM site.**

Test for Systemic Exposure

- $R = \frac{|\#Blood\ Samples > LLOD|}{|\#Total\ Blood\ Samples\ |}$
- Definition: no systemic exposure if $R < 0.05$



US Zovirax
Very high dose
of 50 mg/cm^2

Methodology

- 6 subjects, 6 application sites
- 10,000 bootstrap estimates were computed
- creation of confidence interval for the true population value of the test statistic R
- a one-sided 95% confidence interval was constructed

Results

MIN	MEDIAN	P90	P95	P99	MAX
0	0.012821	0.025641	0.038462	0.051282	0.064103

dOFM
Quality management systems

✓ **High quality standards are key to reliable skin PK studies.**

GCP

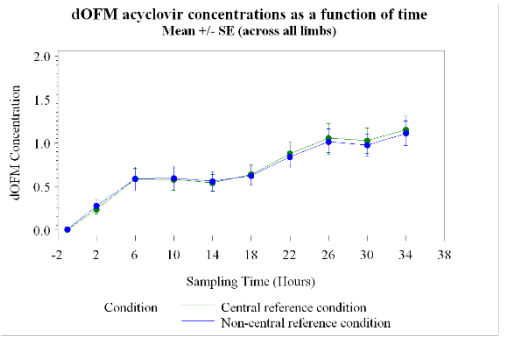
Data Management Plan

eCRFs
SDFs

XLSX → Processing Laboratory Source Data → Mapping Subject ID ↔ OID → CDISC ODM → Import into OpenClinica eCRF → OpenClinica Database

Statistical Analysis Plan

Software Verification and Validation Report
Software Verification and Validation Report
OFMLabData Import Validation Plan
OFMLabData Import Validation Report
OFMLabData Import SPOs

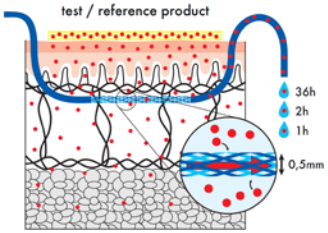


GLP lab

Method Validation Plan
Method validation Report
Method SOPs
Study Analysis Plan

dOFM
Controlled or Monitored Parameters

✓ **Highly controlled set-up has been developed.**



Variations may result from differences in

Trauma formation	➔	**Controlled by cooling**
Application site	➔	**Controlled by application template**
Dosage application	➔	**Controlled by standardization**
Probe depth	➔	**Monitored by ultrasound**
Flow rate	➔	**Monitored by sample weight**
Local blood flow	➔	**Monitored by glucose marker**
Lateral diffusion and cross-talk	➔	**Negligible**
Systemic absorption and cross-talk	➔	**No systemic exposure**

Comparative IVRT study
Investigated drugs

✓ **All investigated 5% acyclovir creams.**

- Reference product Zovirax cream 5% (GSK, U.S.) was compared against itself and six test products:
  - Zovirax cream 5% (GSK, Vienna, Austria)
  - Zovirax ointment 5% (GSK, U.S.)
  - Aciclostad 5% (STADA, Austria)
  - Aciclovir 1A Pharma Cream 5% (1A Pharma, Austria)
  - Antiviral cold Sore cream 5% (Boots, UK)
  - Zovirax cold Sore cream 5% (GlaxoSmithKline, Brentford, UK)

- Statistical method:
  Mann-Whitney U test according to
  USP general chapter <1724>

Comparative IVRT study
Apparatus qualification

✓ **IVRT apparatus qualification was passed successfully.**

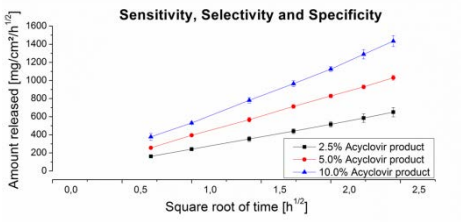
PARAMETER	ACCEPTANCE CRITERIA		RESULTS		
	Intercell Variability (Precision)	Accuracy	Range of variation V	Mean	Pass
Volume of the cells	V ≤0.48 mL[1)]	$\bar{x}_i \in [12 + 0.6\,mL, 12 - 0.6\,mL]$ $for\ 1 \leq i \leq 6$[4)]	0.33 mL	9.77 mL	No
Diameter of the orifice	V ≤0.45 mm[2)]	$\bar{x}_i \in [15 + 0.75\,mm, \quad 15 - 0.75\,mm]$ $for\ 1 \leq i \leq 6$[4)]	0.05 mm	15.01 mm	Yes
Temperature of the receptor medium	-	$\bar{x}_i \in [32 + 1\,°C, \quad 32 - 1\,°C]$ $for\ 1 \leq i \leq 6$	0.23 °C	31.98°C	Yes
Speed of the magnetic stirrer	V ≤ 12 rpm[3)]	$\bar{x}_i \in [600 + 60\,rpm, \quad 600 - 60\,rpm]$ $for\ 1 \leq i \leq 6$[5)]	1.77 rpm	597.98 rpm	Yes
Dispensed sampling volume	-	$\bar{x}_i \in [500 + 15\,\mu L, \quad 500 - 15\,\mu L]$ $for\ 1 \leq i \leq 6$[3)]	10.76 µL	492.40 µL	Yes

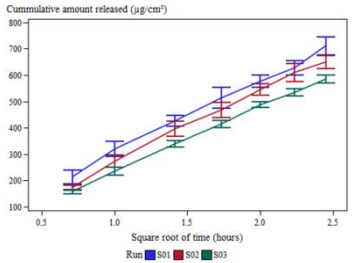
„A Comprehensive Approach to Qualify and Validate the Essential Parameters of an In Vitro Release Test (IVRT) Method for Acyclovir Cream, 5%“ – published online Tiffner et al. **International Journal of Pharmaceutics – OPEN ACCESS**

Comparative IVRT study
IVRT method validation

✓ **IVRT method validation for acyclovir was passed successfully.**

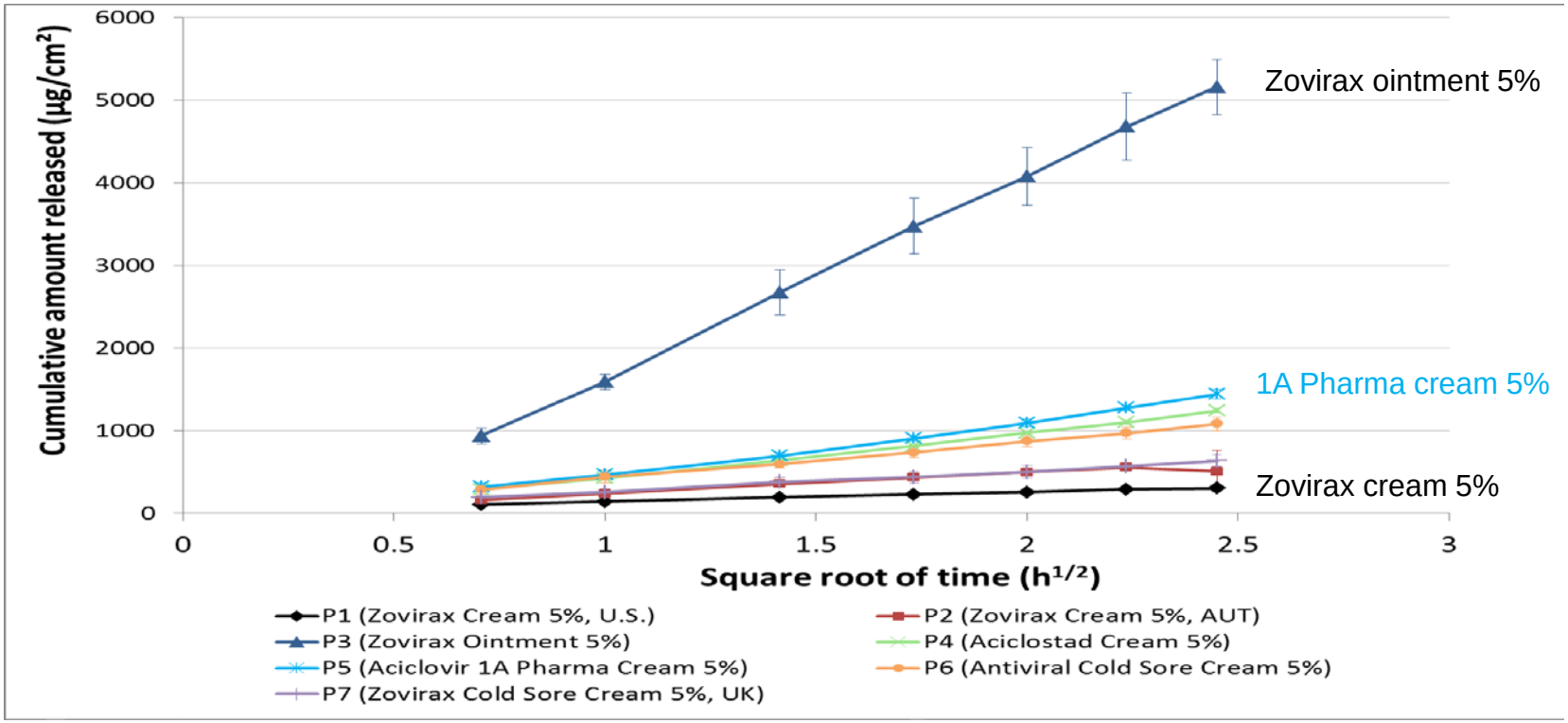
Parameter	Acceptance Criteria	Passed
Membrane Inertness	No acyclovir binding on the membrane: Recovery of 105.5%	✓
Receptor medium solubility	Solubility > 10 times higher than the maximum acyclovir concentration in the receptor medium observed during the IVRT study	✓
Linearity	Lowest R^2 : 0.97, no outlier	✓
Precision and Reproducibility	Inter-run variability 5.8%; intra-run variability 4.4%	✓
Sensitivity	Mean release rate increased with increasing acyclovir concentration	✓
Specificity	Linear regression model (release rate versus product concentration) R^2 =0.943	✓
Selectivity	IVRT method accurately identify in-equivalent and equivalent acyclovir products	✓
Robustness	Release rate for temperature and stirring speed variation deviate < 15%	✓
Recovery	< 10%; no excessive acyclovir depletion	✓





Comparative IVRT study
Results

✓ **IVRT identified different drug release rates.**



dOFM
Clinical Study Details

- ✓ **Test and Reference are both 5% acyclovir creams but NON-Q1**
- ✓ **IVRT: identical release R:R and non identical release T:R**

Zovirax (R) (USA)	Aciclovir-1A (Austria)
Water	Water
Propylene glycol	Propylene glycol
Mineral oil	Viscous Paraffin
White petrolatum	White Vaseline
Cetostearyl alcohol	Cetyl alcohol
SLS	Not disclosed
Poloxamer 407	Not disclosed
Not disclosed	Dimethicone
Not disclosed	Glyceryl Mono Stearate
Not disclosed	Polyoxyethylene stearate

Non-Q1

Equivalence comparison	Computed confidence interval	
	Lower Limit [%]	Upper Limit [%]
Zovirax cream 5% US v. Zovirax cream 5% US	85.7	103.02
Zovirax cream 5% US v. Aciclovir 1A Pharma Cream 5%	16.27	19.60

Acceptance limits: [75%, 133.33%]

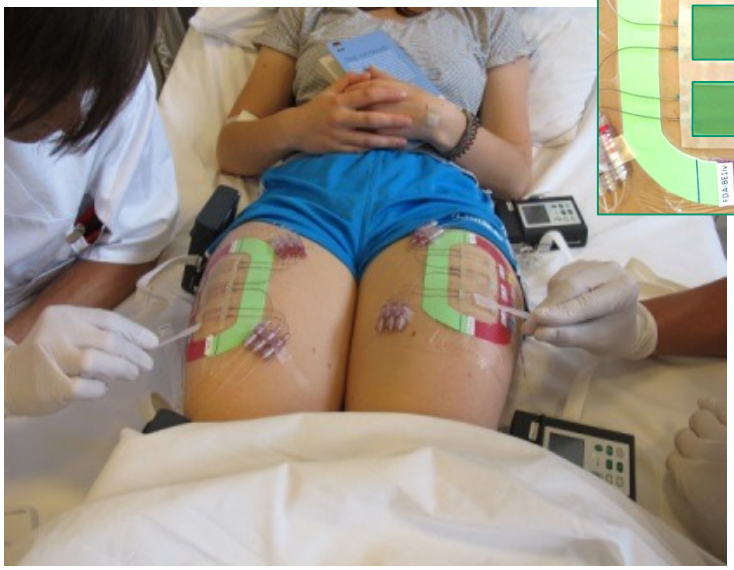
Clinical Bioavailability

Clinical BE Study

Overall AIM: Investigate the capability of dOFM to address BE and non-BE of topical formulations in-vivo.

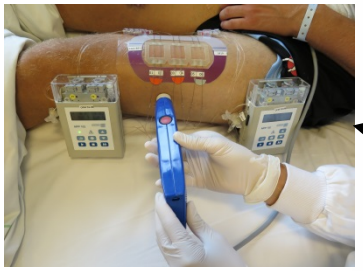
Overview Clinical Studies:

- 20 healthy subjects
- **R**eference: Zovirax® US
- **T**est: Aciclovir-1A Pharma Austria
- 2 application triplets per subject
- 15 mg/cm^2 cream application
- 36 hours dOFM sampling time

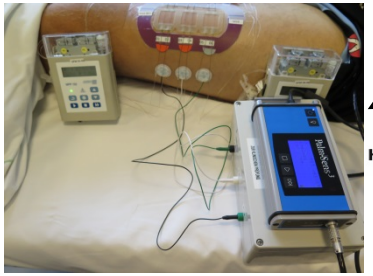


dOFM
Clinical Study Details

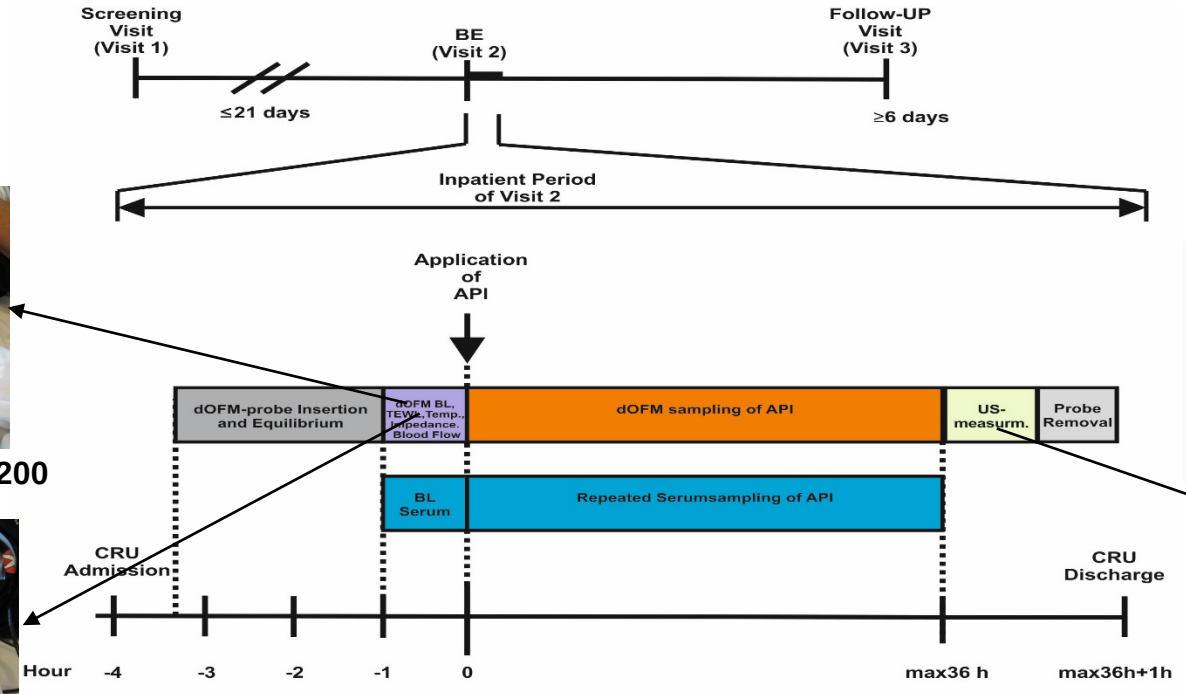
✓ **Highly standardized clinical BE study design.**



TEWL by Aquaflux AF200



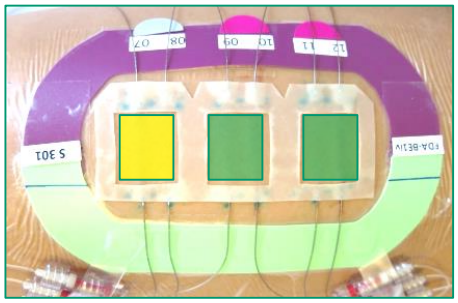
Impedance by JOANNEUM

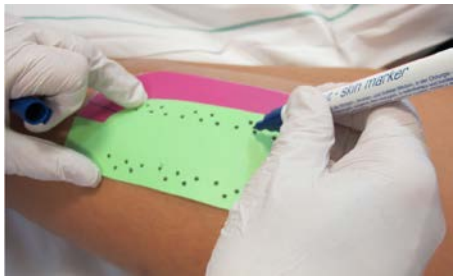


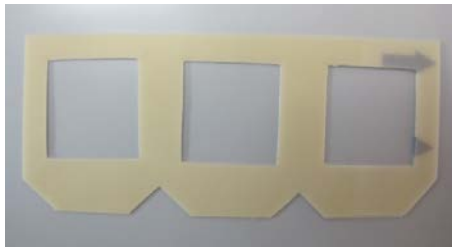
Ultrasound GE-Healthcare

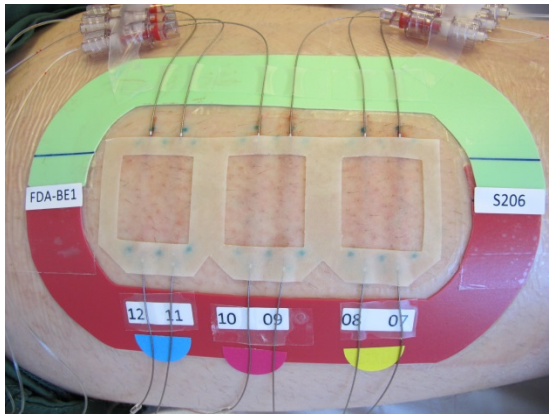
Clinical Bioavailability
Clinical BE Study

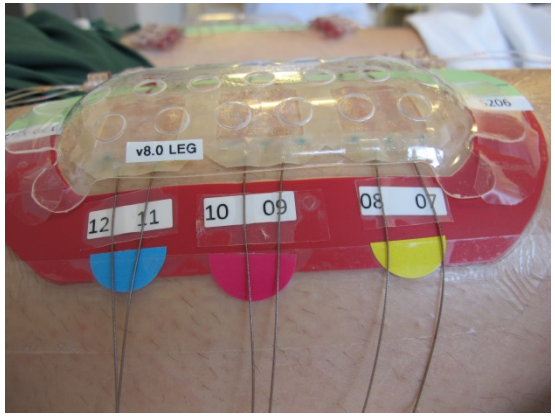
✓ **All procedures are standardized by using templates and SOPs.**

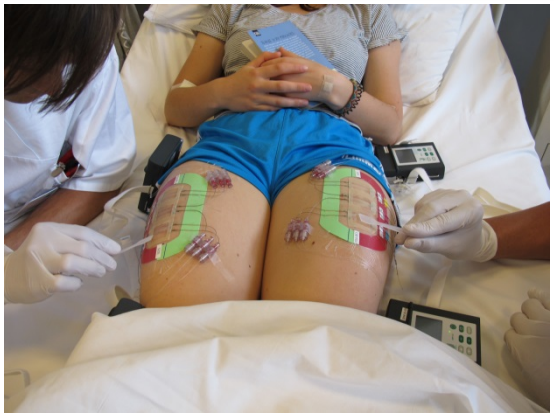


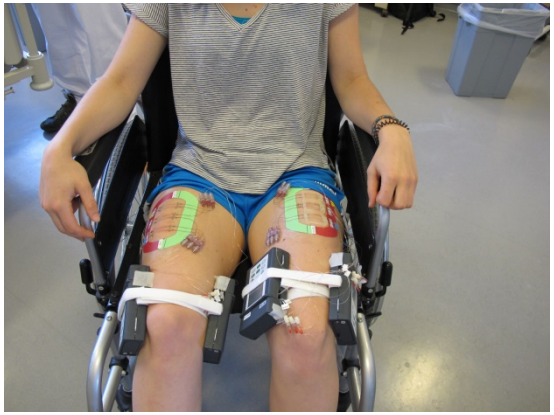


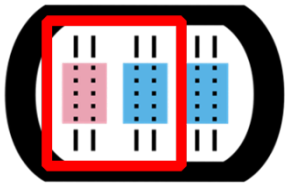






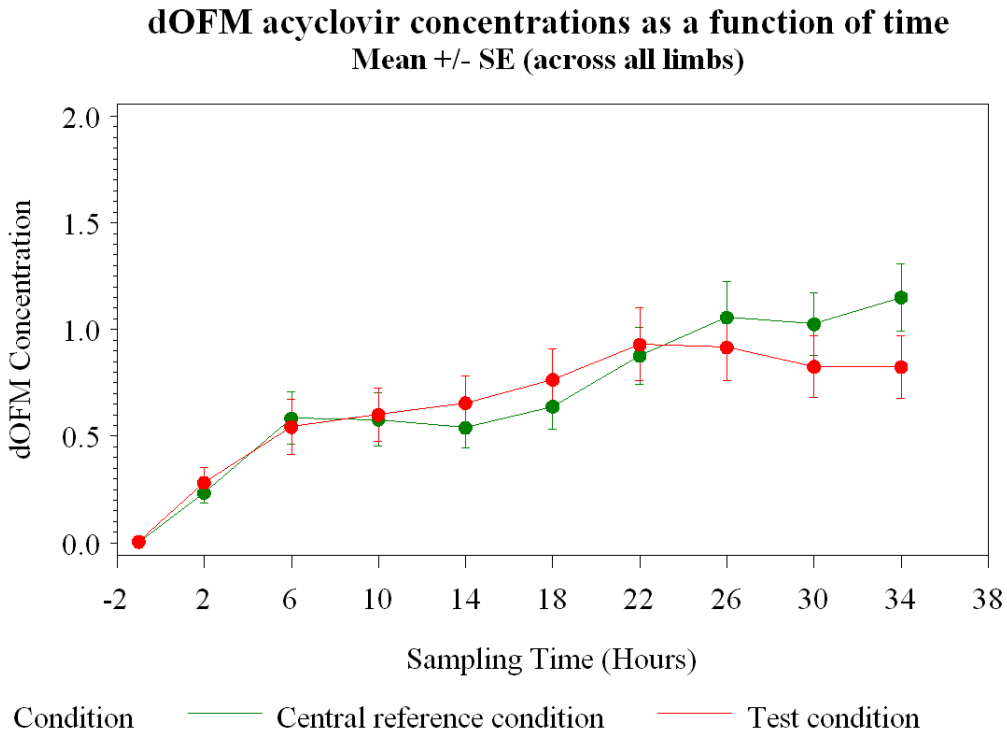




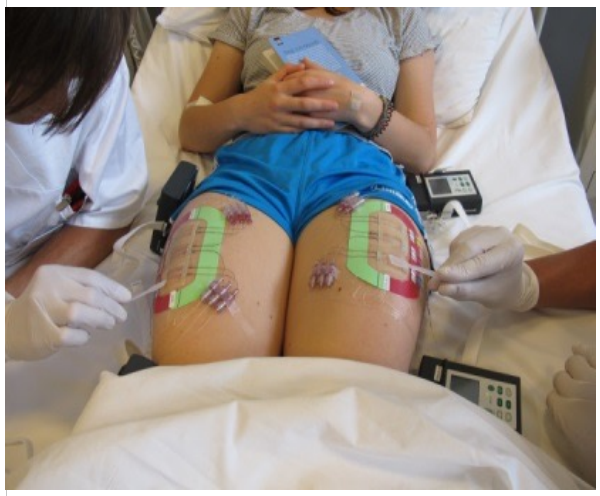


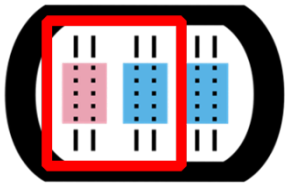
Clinical Bioavailability
Test versus Reference

✓ **Bioavailability: AUC and T_{max} of Aciclovir 1A are highly reproducible**
AUC and T_{max} of Zovirax US are highly reproducible



20 healthy subjects





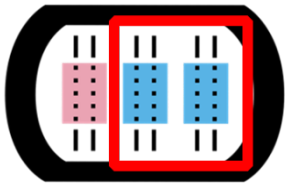
Clinical Bioavailability
Test versus Reference

- ✓ **BA is different for Aciclovir 1A vs Zovirax US based on AUC**
- ✓ **BA is different for Aciclovir 1A vs Zovirax US based on C_{max}**

Outcome variable	$CI_{90\%}$	BE-limits	$CI_{90\%}$ within BE-limits
log(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]	[-0.223 ; 0.223] or [80% ; 125%]	x Failed
log(C_{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]		x Failed

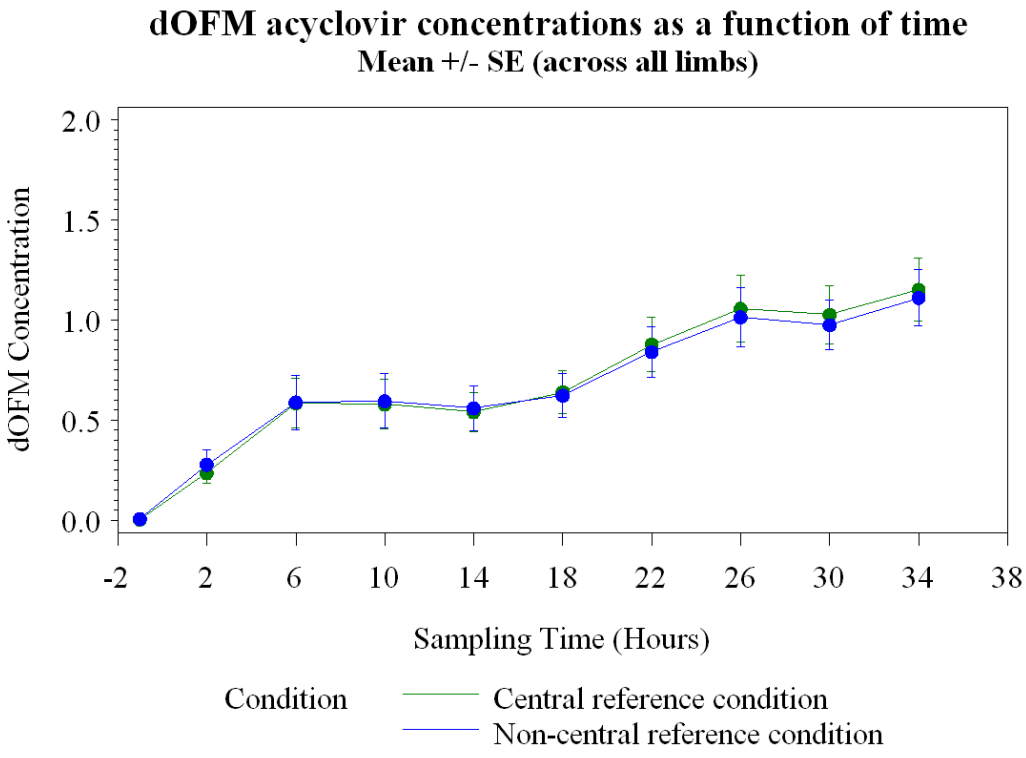
BA is tested for the difference of the log-transformed outcome variables (AUC, C_{max}) between test and reference condition

BA is established if $CI_{90\%}$ falls within the limits of log(0.8)=-0.223 and log(1.25)=0.223 (cf. FDA Guidance For Industry)

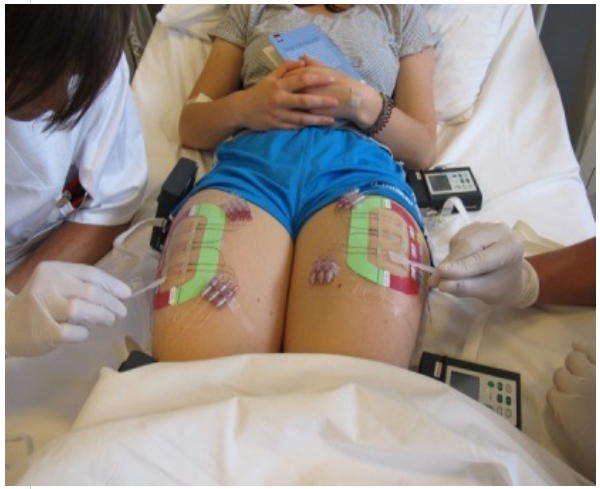


Clinical Bioavailability
Reference versus Reference

✓ **Bioavailability: AUC and C_{max} of Zovirax US are highly reproducible.**



20 healthy subjects



"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**

Clinical Bioavailability
Reference versus Reference

- ✓ **Same BA for Zovirax US vs Zovirax US based on AUC**
- ✓ **Same BA for Zovirax US vs Zovirax US based on C_{max}**

Outcome variable	$CI_{90\%}$	BE-limits	$CI_{90\%}$ within BE-limits
log(AUC0-36h)	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]	[-0.223 ; 0.223] or [80% ; 125%]	**passed**
log(C_{max})	[-0.155 ; 0.190] or [85.7 % ; 120.9%]		**passed**

BA is tested for the difference of the log-transformed outcome variables (AUC, C_{max}) between the two reference conditions

BA is established if $CI_{90\%}$ falls within the limits of log(0.8) = -0.223 and log(1.25) = 0.223 (cf. FDA Guidance For Industry)

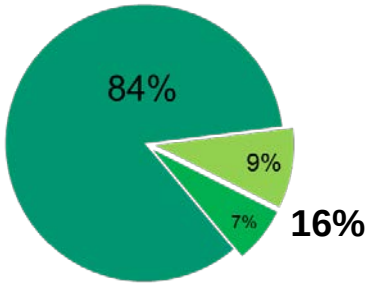
Skin penetration insights
Total variability

✓ **BE study set-up shows low intra-subject variability.**

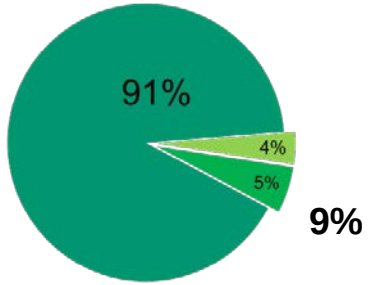
Total $CV_{logAUCacyc}$ was **39% - 44%** (41% Microdialysis Benfeldt et al.)

Components of total CV (ANOVA):

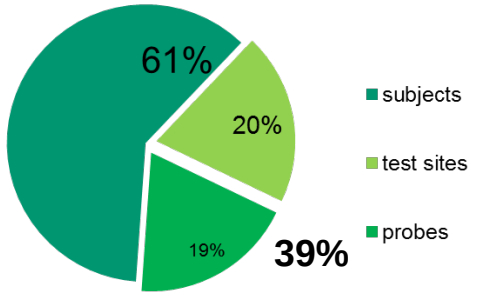
- Inter-subject variability: 84-91% OFM (61% Microdialysis Benfeldt et al.)
- Intra-subject variability: 9-16% OFM (39% Microdialysis Benfeldt et al.)



logAUC Zovirax®



logAUC Aciclovir 1A Pharma



logAUC lidocaine MD (Benfeldt et al.)

Benfeldt et al., J Invest Dermatol. 2007 Jan;127(1):170-8. Epub 2006 Jul 27

Pharmacokinetics-Based dOFM
Summary

dOFM in-vivo

- is a reproducible, accurate and sensitive method.
- shows very low method variability.
- reflects in-vivo skin penetration in dermis.
- gives advanced skin penetration insights.

dOFM in-vivo

- can be used to investigate BE on a pharmacokinetic basis.
- could be a useful tool to conduct clinical bioequivalence studies in a small number of healthy subjects.
- is a potential tool to reduce time and costs of clinical bioequivalnce studies.

Clinical Bioavailability
Outlook

Clinical OFM study A: In-Depth Identification of Influencing Factors of Skin Penetration - Moderate Lipopilic/Protein Bound Drugs

- Pilot (n=6): systemic adsorption and cross-talk; lateral diffusion and cross-talk, sample time for C_{max} and ¾ of AUC
- Main study (n=38): investigate BE of (a) RLD to itself, (b) approved generic product to RLD, (c) non-BE product to RLD, (d) BE identify influencing factors

➔ **Optimization of screening and OFM BE study design**

Clinical OFM study B: Standardized BE Study - Highly Protein Bound Drug

- Pilot (n=6): systemic adsorption and cross-talk; lateral diffusion and cross-talk, sample time for C_{max} and ¾ of AUC
- Main study (n=20): investigate BE of (a) RLD to itself, (b) approved generic product to RLD, (c) non-BE product to RLD

➔ **Validate OFM as an universal tool for BE studies for topical drugs**

A big Thanks to…

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Clinical dOFM BE Study

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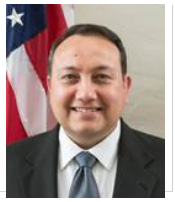
Analytics

Thomas Pieber
Clinical PI

Isadore Kanfer
BE Conultant Expert



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Priyanka Ghosh
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Elena Rantou
Youngsook Lee
Lisa Ko
Jill Coker
and other….

Close Cooperation

Joanneum Research - Medical University of Graz

58 general wards (~1,400 beds)	80,000 patients/year
10 intensive care units (~140 beds)	10,000 patients/year
16 outpatient clinics	500,000 patients/year

One-Stop-Shop
for tissue specific PK and PD

aOFM
adipose-tissue-OFM

cOFM
cerebral-OFM

dOFM
dermal-OFM

IVRT

EN ISO 9001 | EN ISO 13485:2003 | GLP | Data management | statistic

GCP

Preclinical facilities

Mice, rats, rabbits, pigs, sheep

Clinical Facilities
Phase 1-2

- Fully equipped clinical trial center with 12 beds
  - Study performance according to GCP
  - Located at the Medical University of Graz

HEALTH

Bioanalytics and Metabolomics

- Located at the Center of Knowledge and Technology Transfer in Medicine ("ZWT") in Graz
- ~ 20 employees of different disciplines: 50% scientists
- High end bioanalytical lab facility of the HEALTH Institute of Biomedicine and Health Sciences

GLP certified

Thank you for your attention

Dr. Frank Sinner

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