Pushing the Limits of Transdermal Drug Delivery

BIOTTS

Biotts Innovative Transdermal Technology

SAE, London, 11-12 November 2024

Transdermal Drug Delivery

Transdermal drug delivery is a patient-friendly **way of drug (API) administration**, offering a variety of benefits, including:

- Non-invasive, needle-free administration; i.e. improved patient adherence
- Increased bioavailability (vs. oral), i.e. API cost efficiency
- Sustained, constant delivery
- Reduced side-effects

Transdermal Drug Delivery – MTC-Y carrier

Biotts' **proprietary technology platform** offers the following breakthrough benefits:

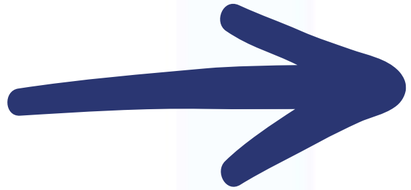
01 Larger molecules like proteins and peptides (up to 6000 Da so far)

02 Both lipophilic and hydrophilic

03 Safety confirmed on humans

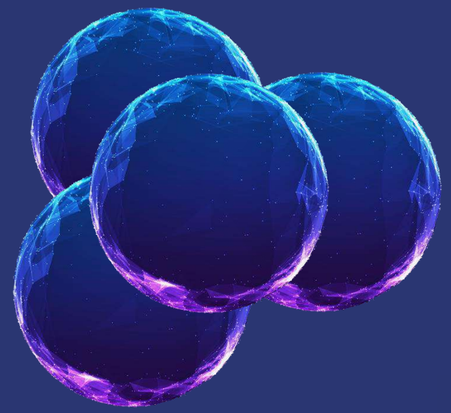
04 Invention protected by 5 patents

05 Versatile toolkit that may be adapted for a large variety of different molecules



Unlimited opportunities for new transdermal therapies

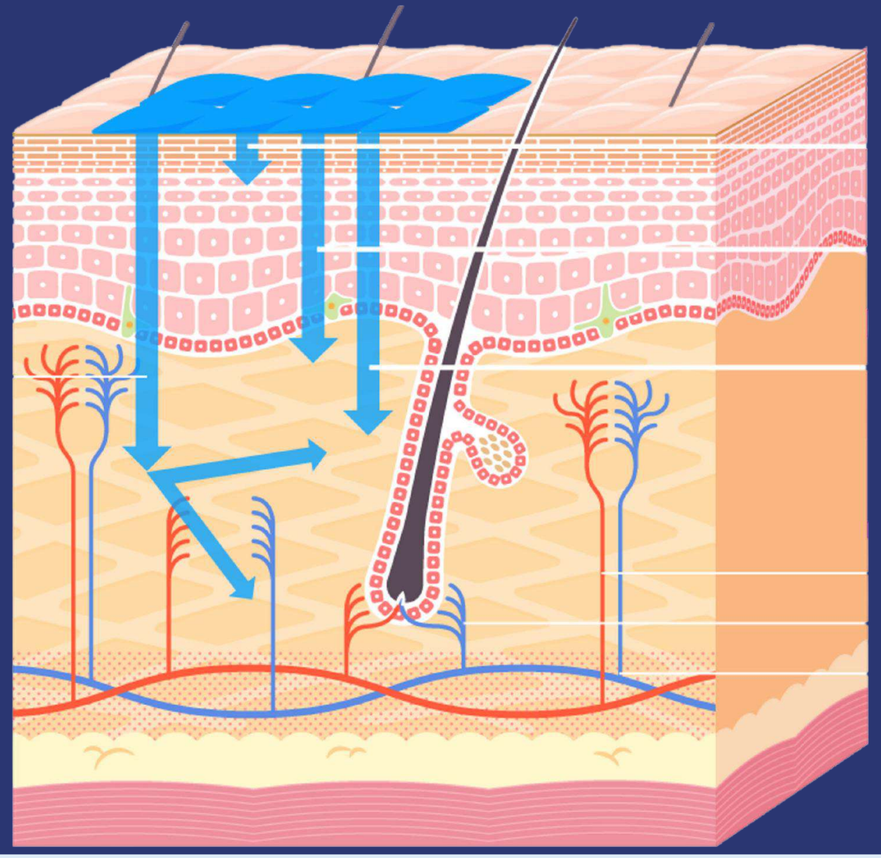
The Biotts MTC-Y carrier technology: a Transdermal Revolution



Targeted delivery

Precise targeting via activation of ionic channels in cell membranes

MTC-Y™M SEMI-SOLID CARRIER



DEEP ABSORPTION

Softens extracellular deposits

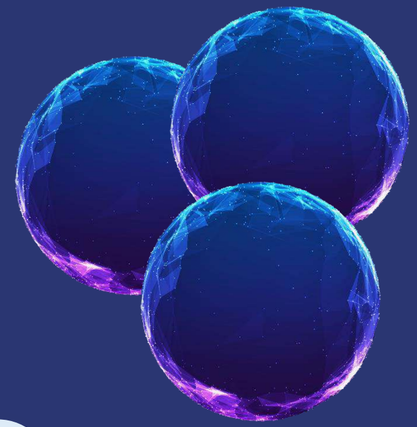
Emulsification enables delivery of hydrophilic and lipophilic drugs

Natural materials promote deeper penetration & absorption

Blood vessels

Nerve receptor

Nerve

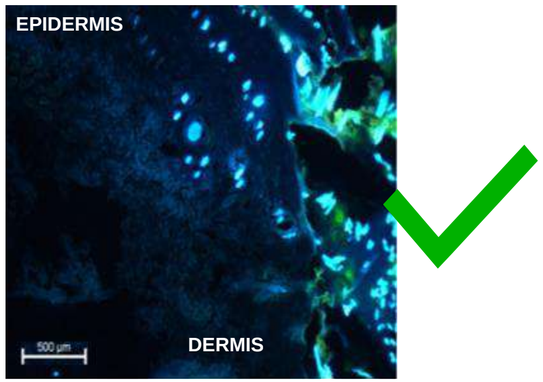


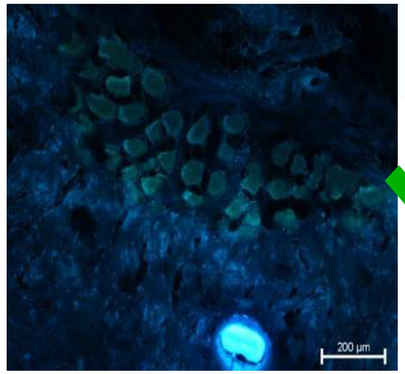
A real game changer in transdermal drug delivery:

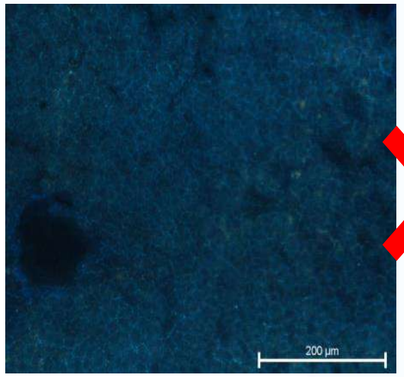
- 8 pharmacopeial excipients forming a spherical cage carrier structure
- Non-invasive; no micro-needles!
- Targeted delivery through skin into blood plasma, synovial fluid etc.

MTC-Y drug delivery technology

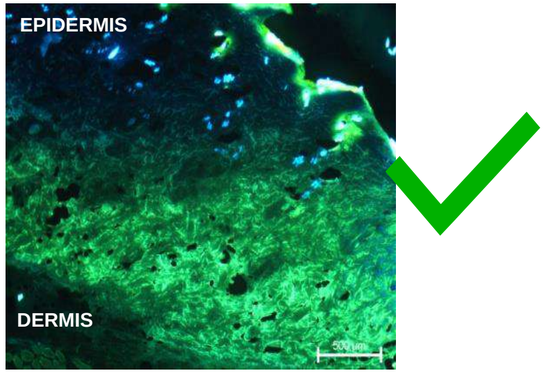
MTC-Y
Medium
activity

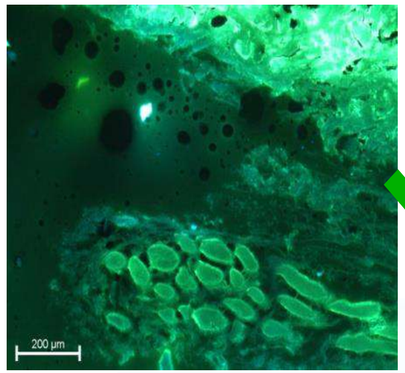


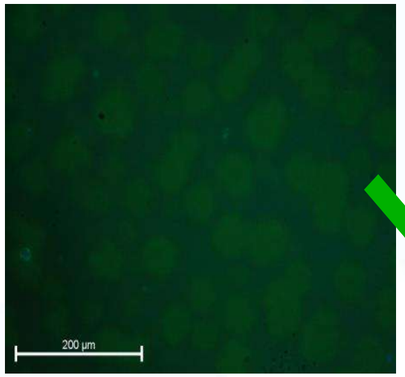




MTC-Y
Deep
activity







Surface & skin

Muscles & tissues

Liver

Full control

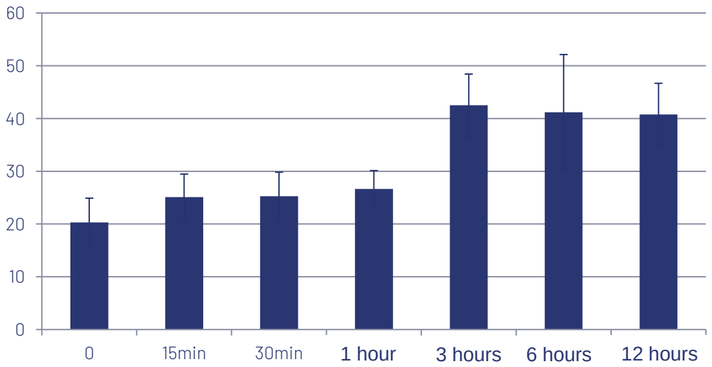
The images present study results on the permeability of the fluorescein-labeled MTC-Y carrier in an animal model. By modifying the substances within the carrier, the absorption depth can be controlled, ranging from the skin surface, through tissues and muscles, to the bloodstream and liver.

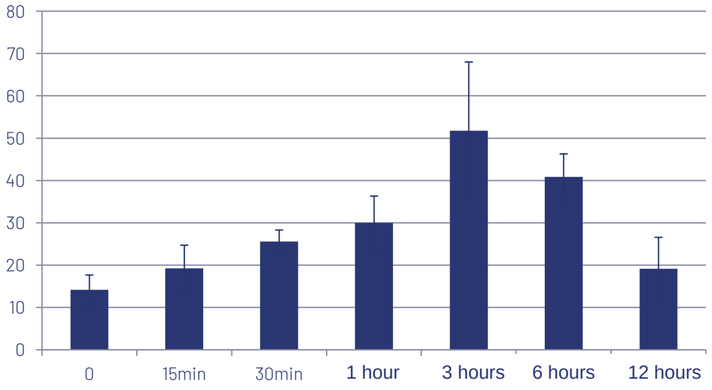
MTC-Y drug delivery technology

MTC-Y
Medium activity

MTC-Y
Deep activity

Diagram of the thickness of the keratinized epithelial layer





Observation of skin histological samples with a fluorescence microscope

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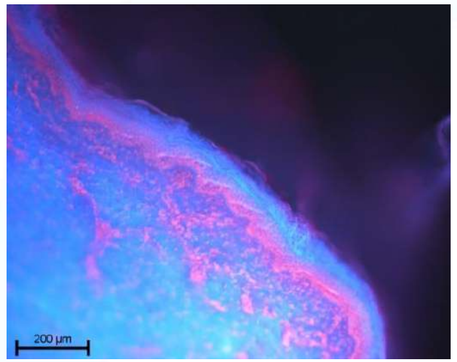
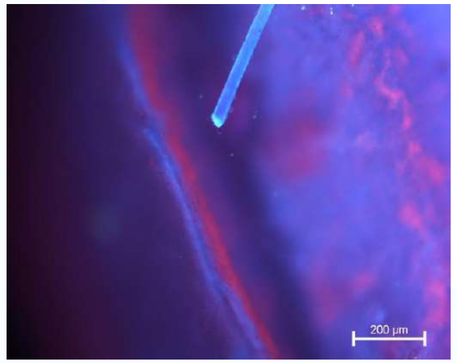
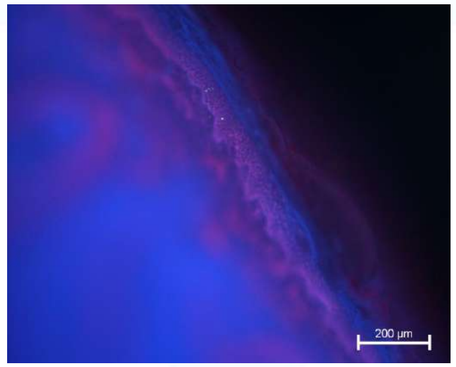
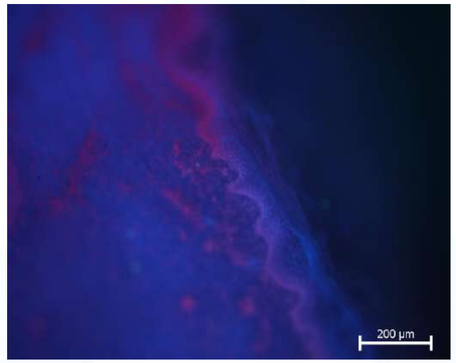




12 hours

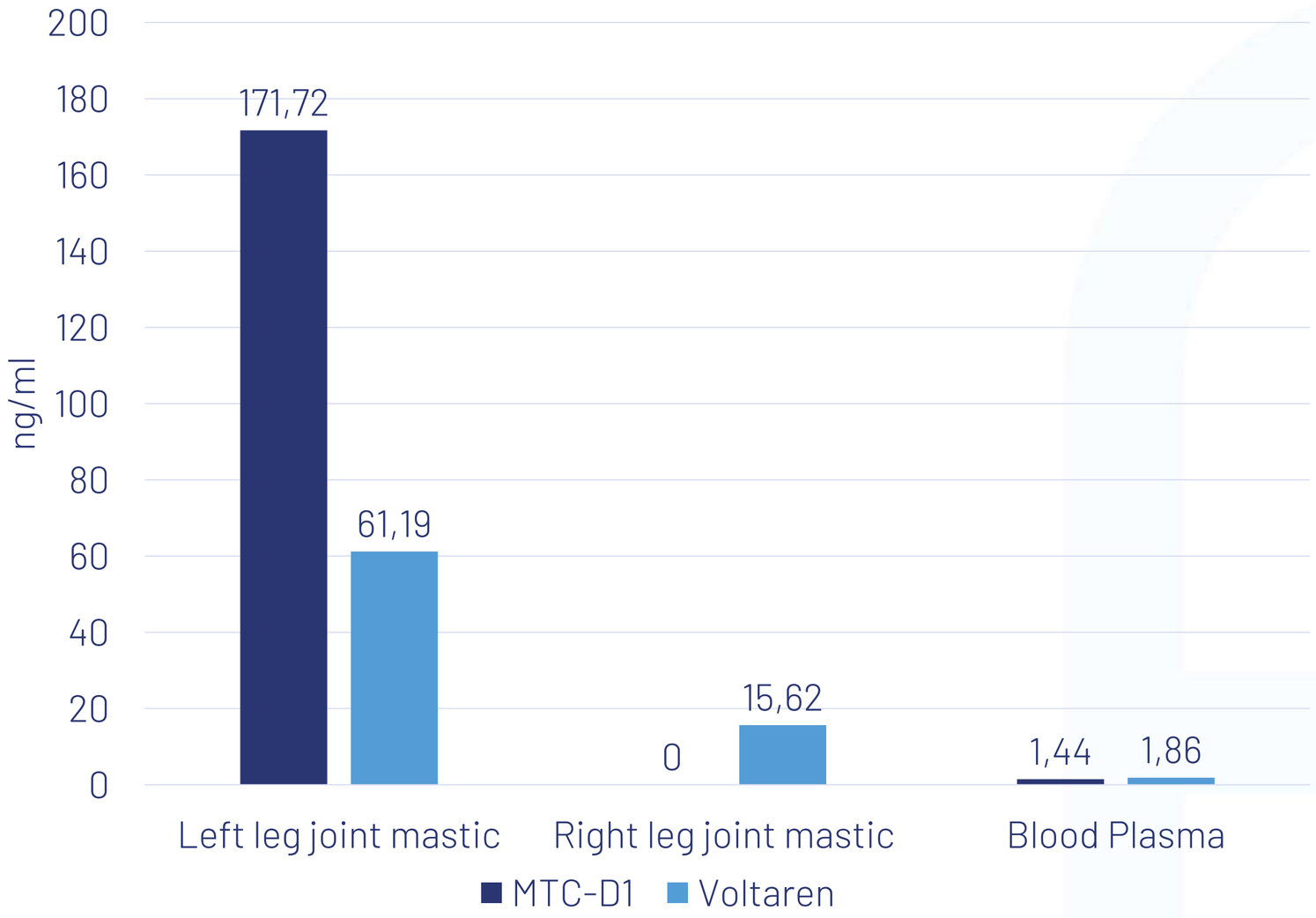




Mechanism of permeation

The images and charts demonstrate how various modifications to the MTC-Y carrier affect the skin's cellular structure and the relaxation of intercellular deposits, enabling the permeation of the MTC-Y carrier with hydrophilic molecules and macromolecular substances.

Comparision of topicaly administrated MTC-NL5(Diclofenac) to Voltaren Max gel



Study design

The study was conducted using :
Biotts MTC-NL5 (diclofenac - **5.5 mg/ml**)
Voltaren Max Gel (diclofenac - **22mg/ml**)

Male pigs were used for the study. Semi-solid products were administered to the left leg only. Puncture of the knee joint was performed 1 hour after application, with prior cleaning of the puncture area. Additionally, blood samples were taken after 1 hour for determination of API (diclofenac) concentration.

Results

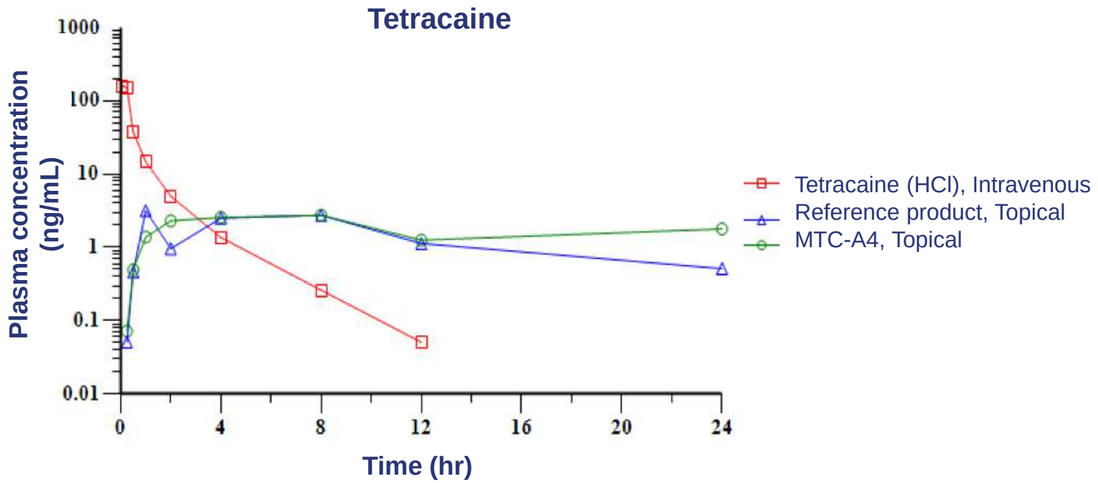
A **2.8-fold higher** concentration of diclofenac was observed in the synovium of the left leg in animals treated with MTC-NL5 compared to animals treated with Voltaren Max Gel.

No diclofenac was observed in the synovium of the right leg in animals treated with MTC-NL5.
Diclofenac at a concentration of 15.62 ng/ml was observed in the right leg of animals treated with Voltaren Max Gel.

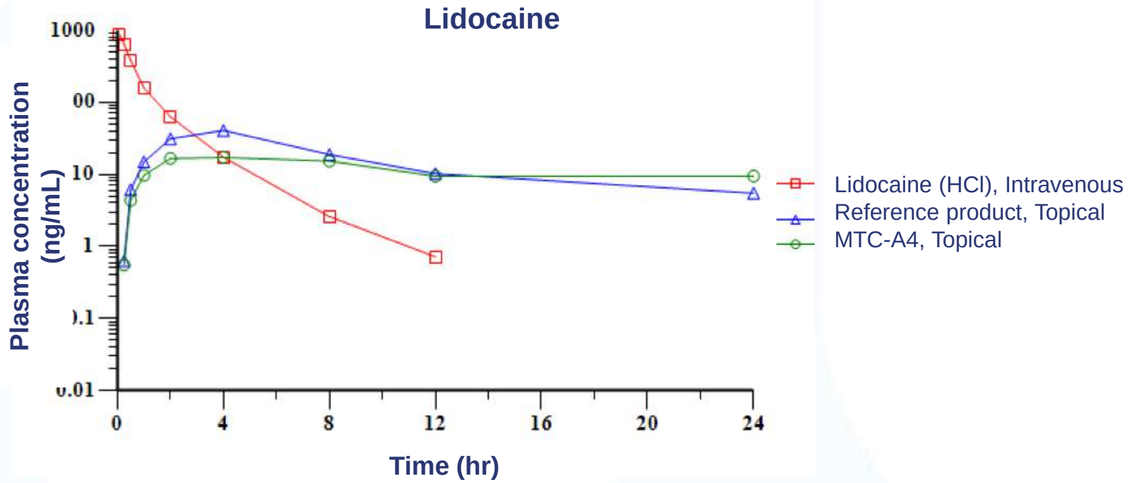
Similar concentration of diclofenac was observed in both the tested groups of animals.

Dermatology – drug candidate MTC-A4 (anesthesia)

This study examined the pharmacokinetics and bioavailability of lidocaine and tetracaine hydrochloride in male Göttingen minipigs, with plasma concentrations measured post-administration.



Average plasma concentration–time profiles of tetracaine after single intravenous (1 mg/kg), or topical (10 g/animal) of reference product and MTC-A4 administration



Average plasma concentration–time profiles of lidocaine after single intravenous (1 mg/kg), or topical (10 g/animal) of reference product and MTC-A4 administration

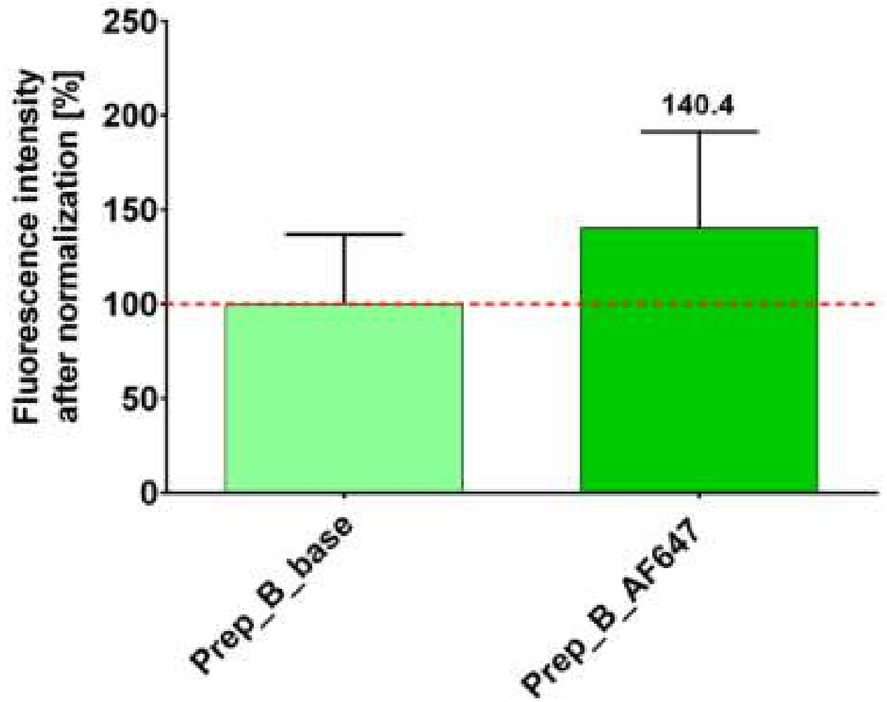
The concentration of the active substances, lidocaine and tetracaine, in the product MTC-A4 is 4% each, while in the reference product it is 7% each. The results show that using lower concentrations of active substances similar bioavailability of the same API was obtained. Another observation is more stable blood concentrations of the active substances released from MTC-A4 after 24 hours compared to the reference product.

Conclusions

Tetracaine showed high clearance and distribution, with a topical bioavailability of 1.26% for the reference product and 3.34% for MTC-A4. It had a longer half-life after topical absorption (6.37 hours) compared to intravenous use (1.85 hours). Lidocaine exhibited moderate clearance and high distribution, with topical bioavailability at 1.41% for the reference and 1.98% for MTC-A4.

Large molecule pilot study

Dermal permeation of an anti-mouse CD3ε antibody conjugated with Alexa Fluor 647 fluorescent dye, encapsulated in our MTC-Y carrier formulation.



Given the selective nature of the encapsulated antibody, the test was conducted in a mouse model. Fluorescence emission for the AF647 dye, excited with a 638 nm laser, was collected to visualize the antibody. Reflected light from the 638 nm laser (624-653 nm) was used to visualize skin layers.

MTC-Y modified carrier, which contained the antibody directed against the murine CD3 antigen labeled with the Alexa Fluor 647 fluorescent dye, increased the fluorescence intensity in the skin by approximately 40%, compared to the control vehicle without antibody.

Total Addressable Markets: Diabetes and Obesity

Market:
US$ 83 billion
TAM annually
by 2030

Diabetes (Type 1 and Type 2)

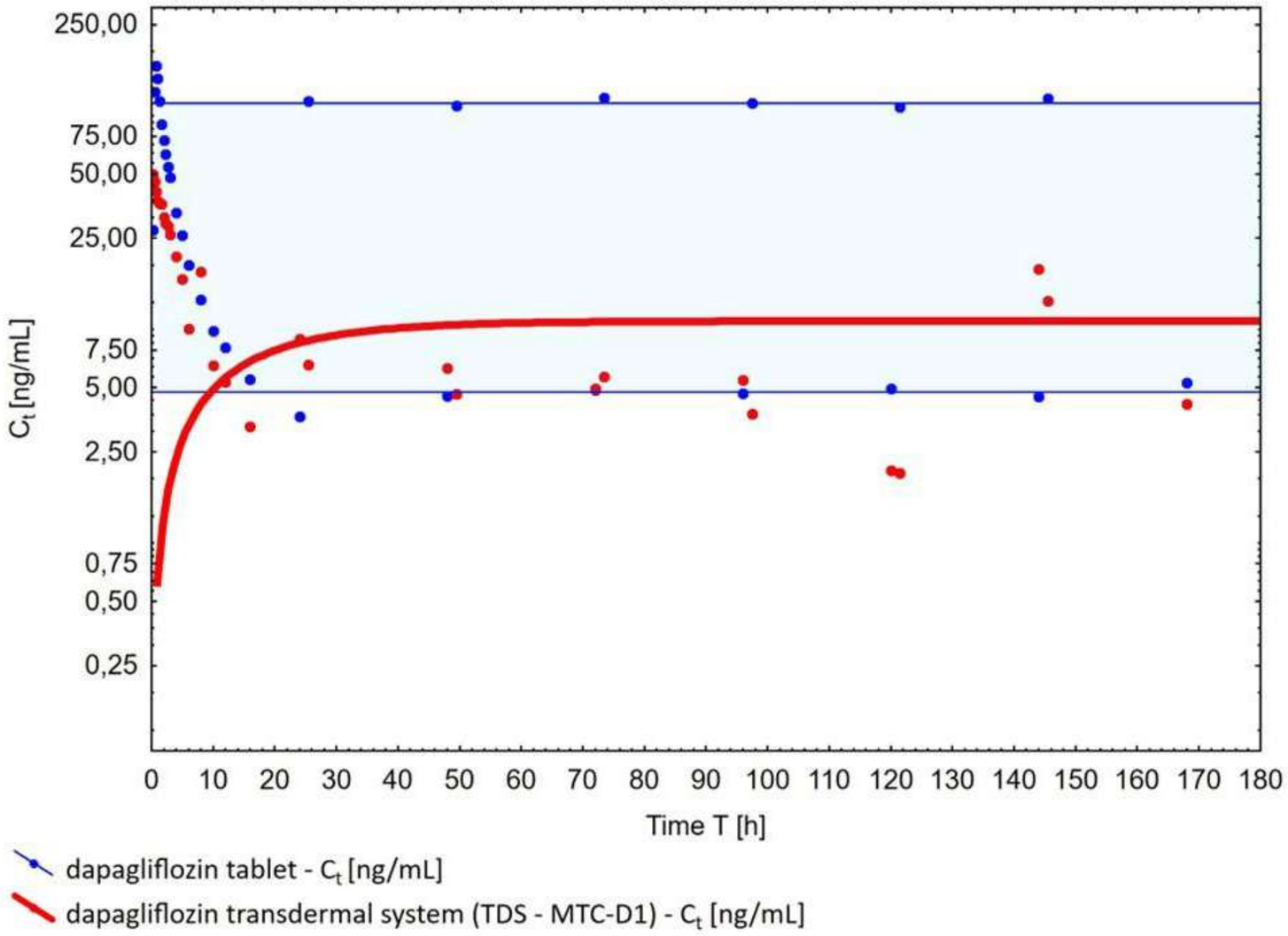
- 462 million patients in 2017, 643 million by 2030
- Insulin: US$ 20 billion in 2022, US$ 23 billion by 2030
- Glucagon-like Peptide-1 Semaglutide: US$ 15 billion in 2022, US$ 60 billion by 2030 (32 million patients)

Obesity

- Sub-market size: est. US$ 30 billion by 2030
- Rapidly developing GLP-1 sub-market as a weight loss miracle drug; clinically proven up to 20% body weight loss, no side-effects
- Average consumer spend in the US for weight loss US$ 1,000 per month, no insurance coverage

Dapagliflozin clinical results

Comparison of oral and transdermal blood plasma concentration LCMS



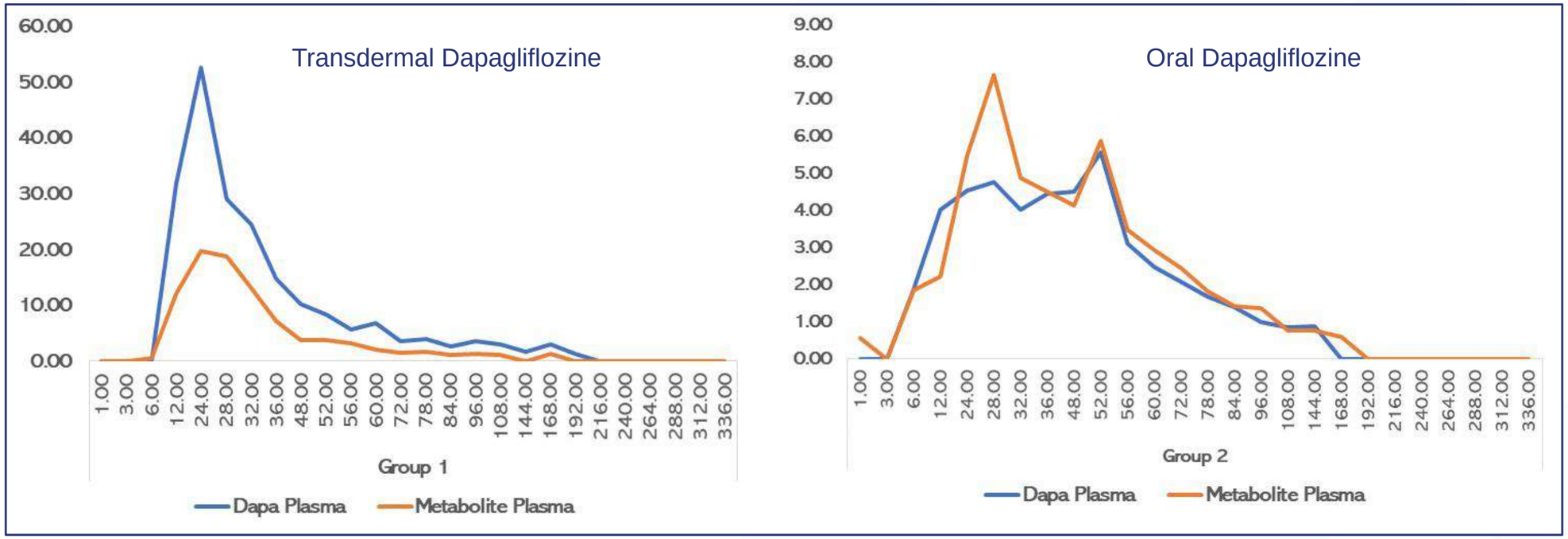
Key takeaways

The effectiveness of the MTC-Y carrier was confirmed in a clinical trial.

The study confirmed both the safety of Biotts transdermal technology and its therapeutic effectiveness.

Diabetology – drug candidate MTC-D1 (Dapagliflozin)

The concentrations of Dapagliflozin-metabolite in plasma were detectable in-parallel to that of Dapagliflozin after application of the transdermal system, which suggests the simultaneous metabolism of the active drug, example:



This contrasts with the Dapagliflozin oral kinetics, where there is the extensive metabolism by liver, colon, and small intestine resident UGT1A9s and the fraction of circulating inactive Dapagliflozin-metabolite is way more than Dapagliflozin.
This confirms that a major metabolic checkpoint (first-pass metabolism) has been evaded via transdermal approach and much less drug would be required in the patch to get the therapeutic efficacy.

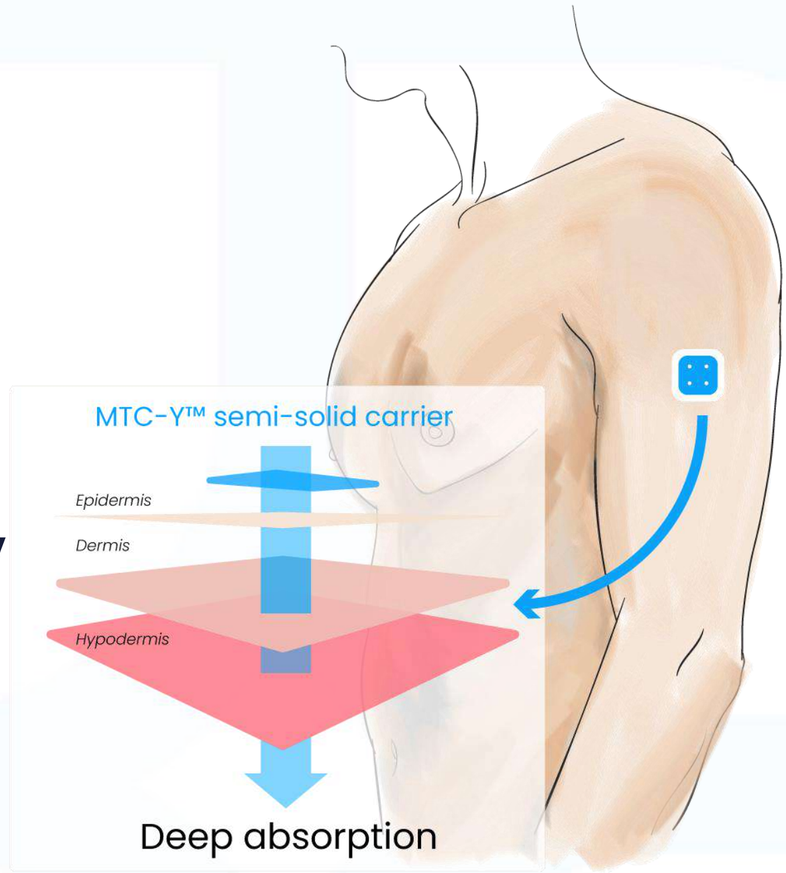
Our Focus Products / Key Assets

Insulin Patch: a patch for (basal long-acting) insulin needs

- Sustained 5 days activity; replacing 10 injections
- Reduced medical waste
- Improved hygiene

Semaglutide Patch: a weekly patch for Diabetes T2 & Obesity

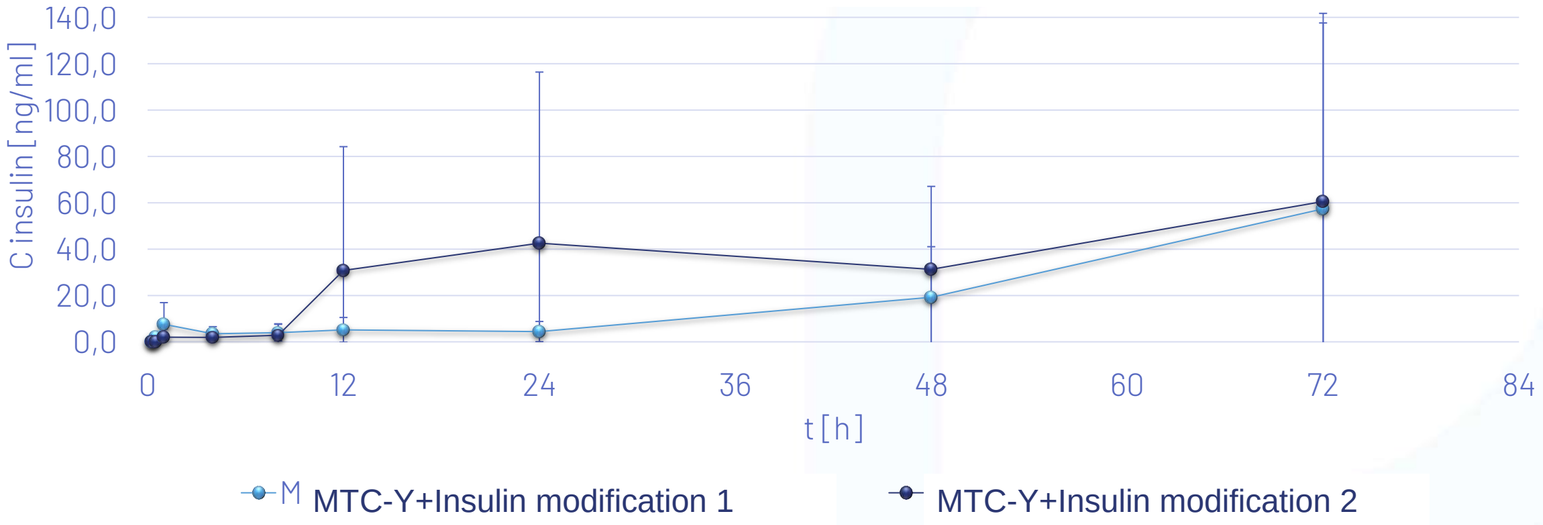
- Convenience; weekly patch vs. daily pill
- Cost; 10 times less API
- No side-effects



Transdermal Insulin formulation in vitro testing

BIOTTS

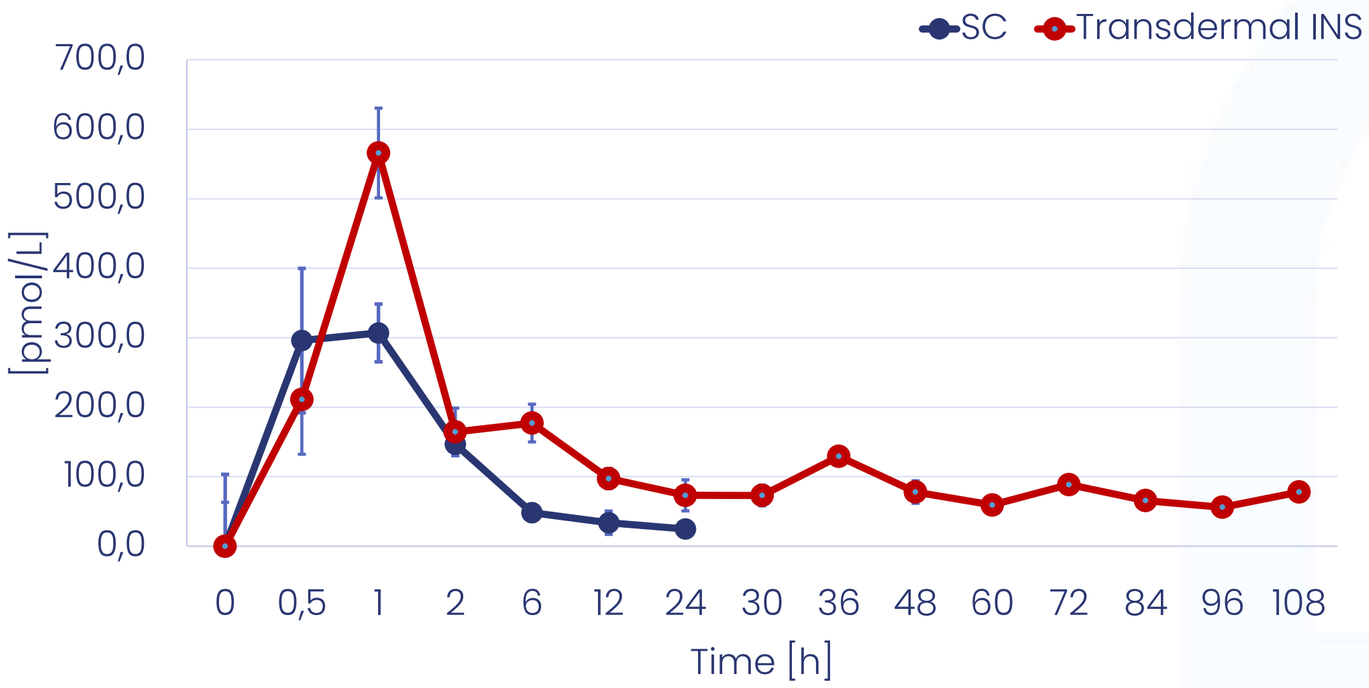
Release analysis, form.: MTC-Y+Insulin modification 1, MTC-Y+Insulin modification2;
Acceptor medium : Phosph. Buffer 7,4+propylene glycol+EDTA+BSA;
Membrane : porcine skin



A porcine skin permeation study (the structure most similar to human skin) confirmed the ability of the MTC carrier to transport insulin through the natural skin barier.

Claim Substantiation: **Insulin**

Transdermal MTC carrier
Insulin Rat Plasma Concentration



Transdermal MTC carrier
Insulin Rat Pharmacokinetics

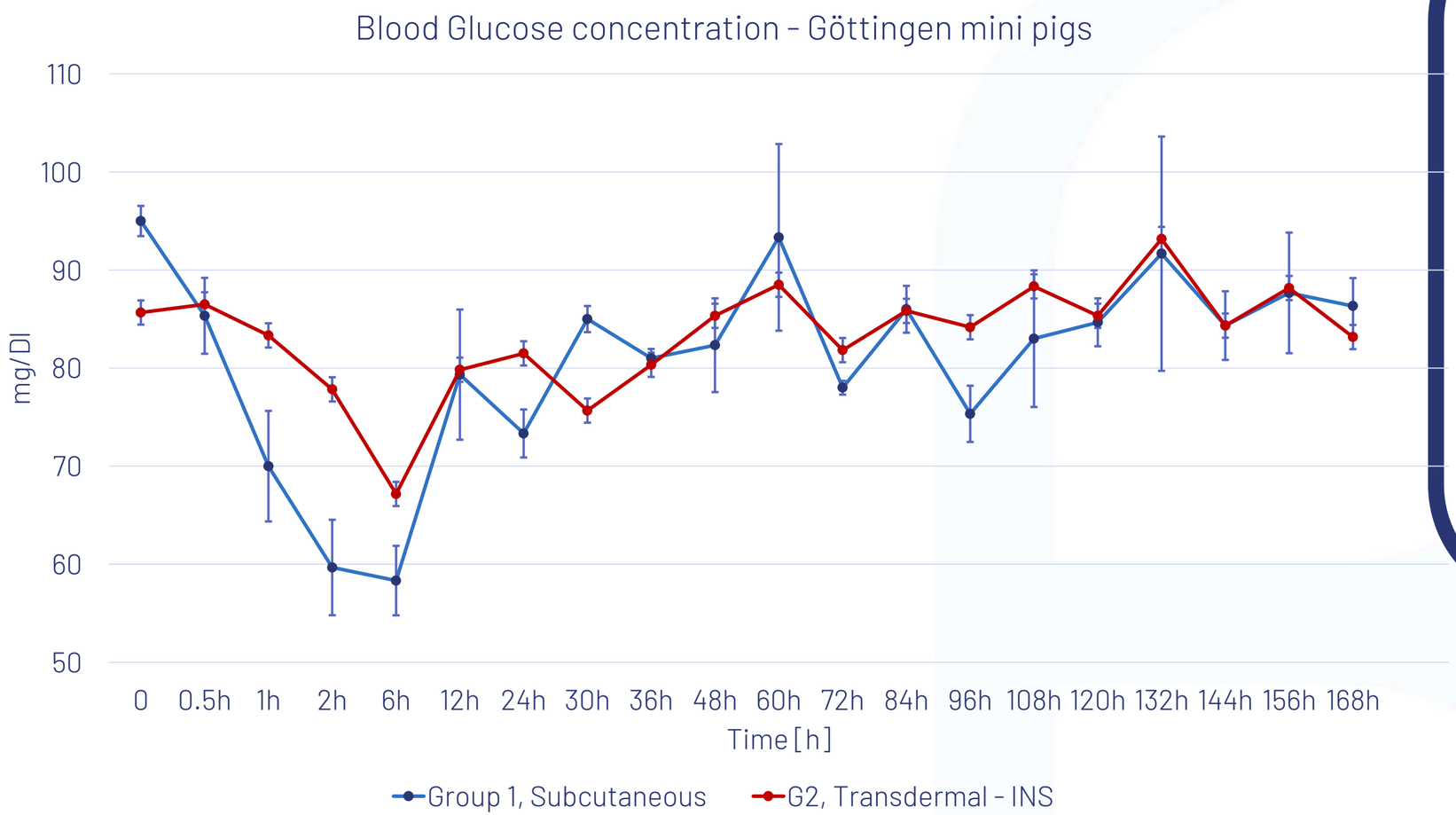
Parameter	Group 1, Subcutaneous	Group 3, Dermal - F-INS
Dose D [mg/Rat] =	0,035	0,350
$T_{1/2}$ [h] =	19,7	
C_{MAX} [pmol/L] =	306,94	565,81
T_{MAX} [h] =	1,0	1,0
MRT [h] =	21,8	62,3
$AUC_{0\rightarrow t=24}$ [pmol·h/L] =	1439,9	3142,4
AUC_{INF} [pmol·h/L] =	2146,4	11820,5
AUC_{INF_TTS} / AUC_{INF_SC} =	5,51	
$AUC_{0\rightarrow t=24\_TTS}$ / $AUC_{0\rightarrow t=24\_SC}$ =	2,18	
F_{REL_INF} [%] =	55,1	
$F_{REL\_0\rightarrow t=24}$ [%] =	21,8	

Key Takeaways:

Transdermal Bioavailability 55%; highest ever reported
Sustained 5-day activity
Improved therapeutics, convenience, cost base

Claim Substantiation: **Insulin**

Transdermal MTC- INS carrier
Glucose Mini-Pig Plasma Concentration



Key Takeaways:

Confirmed activity

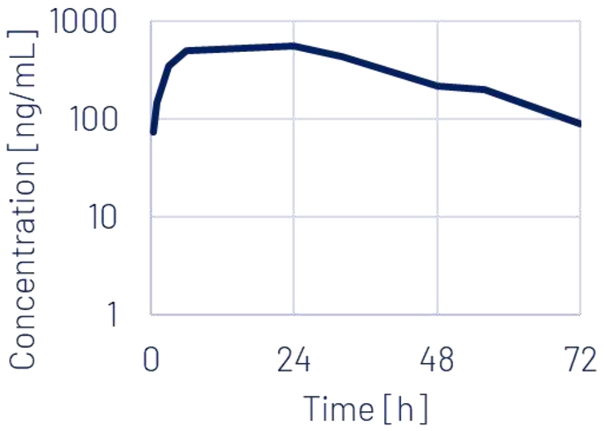
Transdermal effectiveness

70% of SC;after 6 hours in Cmax

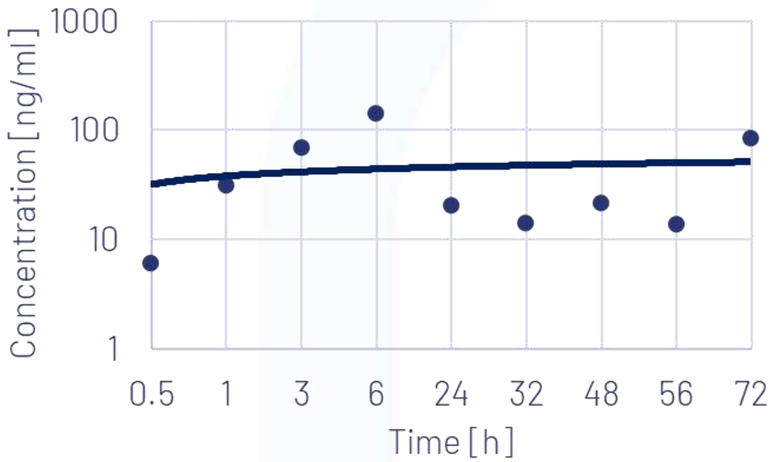
C max in the same time point.

Claim Substantiation: **Semaglutide**

Subcutaneous
GLP-1 Rat Plasma Concentration



Transdermal MTC carrier
GLP-1 Rat Plasma Concentration



	Subcutaneous
Dose [mg/kg]	0,3
C_{MAX} [ng/mL]	**556,0**
T_{MAX} [h]	**24**
$AUC_{0\rightarrow t}$ [ng·h/mL]	24276,26
AUC_{INF} [ng·h/mL]	26642,57
F_{ABC} [%]	**80,5432**

	MTC-Y semi-solid carrier
Dose [mg]	2,0
C_{MAX} [ng/mL]	141,78
T_{MAX} [h]	6,0
$AUC_{0\rightarrow t}$ [ng·h/mL]	2723,58
AUC_{INF} [ng·h/mL]	5575,66
F_{ABC} [%]	4,1222

Key Takeaways:

First time ever that a peptide like Semaglutide is administered through the skin

Bioavailiability 10x higher than oral

Feasible alternative even when compared with injectables

Product Pipeline 2024-2027

INSULIN

Proof of Concept → Pre-Clinical → Clinical Phase 1 → Clinical Phase 3 →

SEMAGLUTIDE

Proof of Concept → Pre-Clinical → Clinical Phase 1 →

OPERATIONS

→ Strategic Partnerships | Scale Up | Market Preparation

GO TO MARKET

Brand Awareness | Distribution Network

BIOTTS

Strategic Partnerships

- Bioton SA for Insulin and initial channel to market
- Bachem for Semaglutide
- LTS Lohmann and ProSolus for patch development, scale-up and manufacturing
- Next steps: commercial partners

BIOTON

BACHEM

LTS

ProSolus
Transforming Transdermal Delivery

Team

Jan H. Hendriks, MSc. MBA – Chief Executive Officer

- Accomplished business leader with a proven track record of 30 years in specialty chemicals and active pharmaceutical ingredients.

Dr. Pawel Biernat – Chief Technology Officer

- Co-founder and co-author of BIOTTS patents and therapeutic systems, 20 years of experience in the field of transdermal drug delivery.

Katarzyna Golab-Levai – Chief Financial Officer

- EY trained certified account with more than 10 of experience in a wide variety of industries, and specialized in international financial reporting and accounting standards

Dr. Gabriele Dallmann – Regulatory Affairs

- Internationally renowned biopharmaceutical expert with more than 25 years of experience in drug development and regulatory affairs of biopharmaceuticals.

Dr. Ewa Micewicz – Clinical Affairs

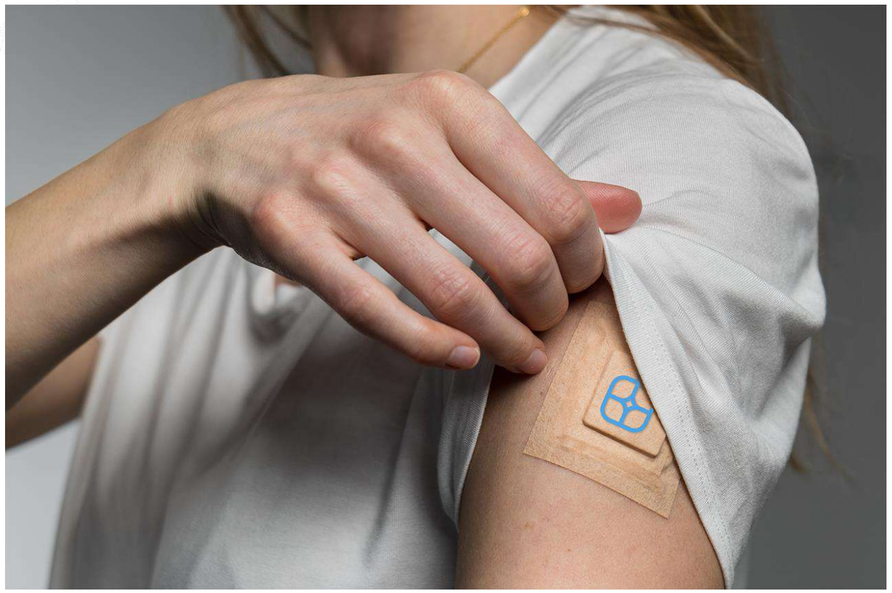
- Established scientist with 20+ years of experience in immunology, virology and radiation oncology research with proven success record of scientific achievements. Extensive experience in in vivo studies utilizing various mouse models. Hands on clinical experience.

Foundation of the team

Wroclaw Medical University
Harvard
IMS Health & Quintiles are now IQVIA
ICI
GLG Pharma
Fresenius Kabi
Ashland always solving
uOttawa
University of Twente The Netherlands
MSM
Grupa Hasco
Noramco
innox.
Roche
SK Capital

Transdermal therapies of diabetes are within reach

Transdermal INSULIN



Transdermal GLP-1

What’s next ……..?

Business Model – Technology Platform

Profit share

Profit share for Insulin

Revenues

Direct revenues from Semaglutide product through distribution network

Premium Pricing

Competitive premium pricing vs. Injectable; directly targeted at patients and consumers

Cost Benefit

Significant cost benefit for patients vs. any oral alternative

Contact

p.biernat@biotts.com

THANK YOU!