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EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE

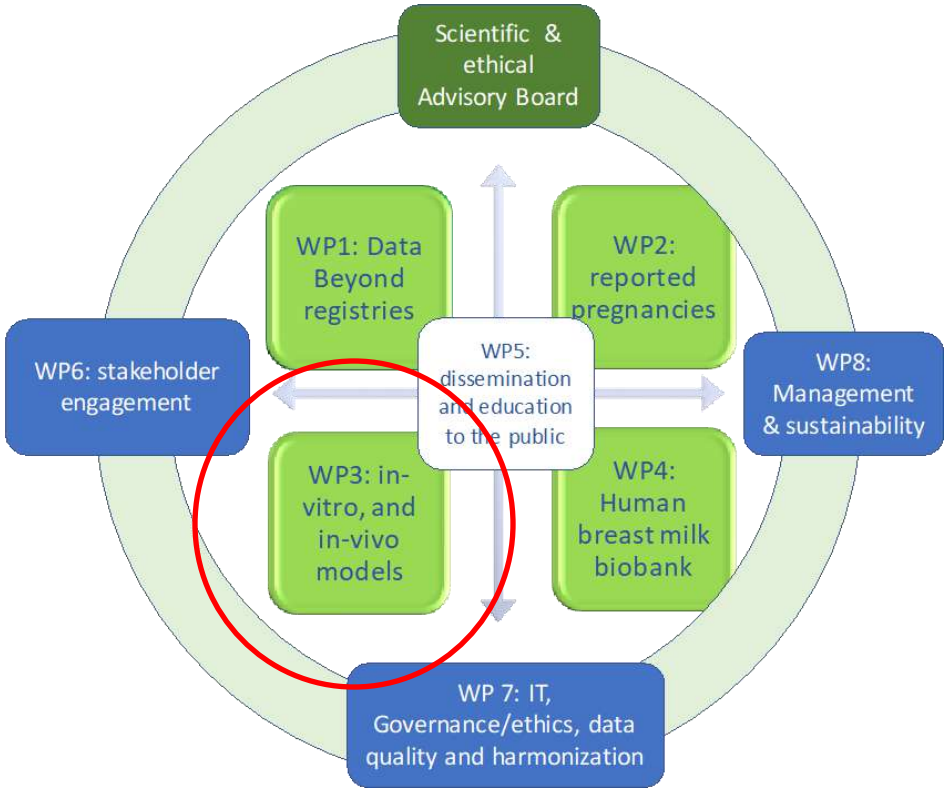
Göttingen minipigs model to study drug milk excretion and breastfed infant drug exposure

Domenico Ventrella, DVM, PhD
ALMA MATER STUDIORUM – UNIVERSITY OF BOLOGNA

EPTRI SCIENTIFIC MEETING 2024 – BARI – 09/07/2024

The ConcePTION project and WP3

Main objective. Determination of drug transfer and infant drug exposure during lactation: generation of quantitative and translatable data



Objective:

Relying on **existing expertise with animal lactation models**, to develop a relevant animal lactation model (along with an in vitro model) in a species sufficiently related to human lactation physiology to validate extrapolation of the human in vitro and animal in vivo data to human in vivo predictions.

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant no. 821520. The contents reflect the ConcePTION project's view and not that of IMI/EU/EFPIA.

In vivo animal model for milk secretion of medicines

- No well-developed non-clinical model accepted by health authorities that can be used to predict medicine secretion into human milk
- The current PPND does not determine drug concentration in milk as a routine endpoint and does not evaluate milk quality or quantity leaving a gap in the testing paradigm

Göttingen Minipigs

- Well characterized model currently used by pharmaceutical companies for general and reproductive toxicology
- Similar anatomy of the mammary gland and lactation physiology when compared to humans
- Refined procedures for repeated blood samplings as well as training protocols available
- "Lower" ethical values in comparison to dogs and NHPs (other candidate species)

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Study design template

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MEDICINE ADMINISTRATION

Daily training

lactation week 3 | lactation week 4

d-30..**d0** d1 d2 **d3** d4 **d5** d6 d7 **d8** **d9** … **d18** **d19** d20 d21 **d22** **d23** d24 **d25** **d26** d27 d28

Parturition

Peri…neter

…aternal m…
…r day

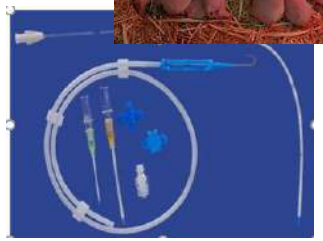
…matched maternal/piglets
…ts per day

…cine admin.

…ne admin.

…nin.

…n.



Generic study design tem…ints, as well as th…
…dicine.

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Chosen medicines and timeponts

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AMOXICILLIN

Dose: 7 mg/kg

Admin route: IM

Timepoints:

SOW DAYS:
- Before medicine admin.
- 2h post-admin.
- 4h post-admin.
- 8h post-admin.

SOW + PIGLETS DAYS:
- Before medicine admin.
- 2h after admin.

METFORMIN

Dosage: 500 mg/kg

850 mg/kg

Admin route: OS

LEVOCETIRIZINE

Dosage: 15 mg/kg

40 mg/kg

Admin route: OS

VENLAFAXINE

Dosage: 75 mg/kg

350 mg/kg

Admin route: OS

SOW DAYS:
- Before medicine admin.
- 1h post-admin.
- 3h post-admin.
- 6h post-admin.

SOW + PIGLETS DAYS:
- Before medicine admin.
- 4h after admin.

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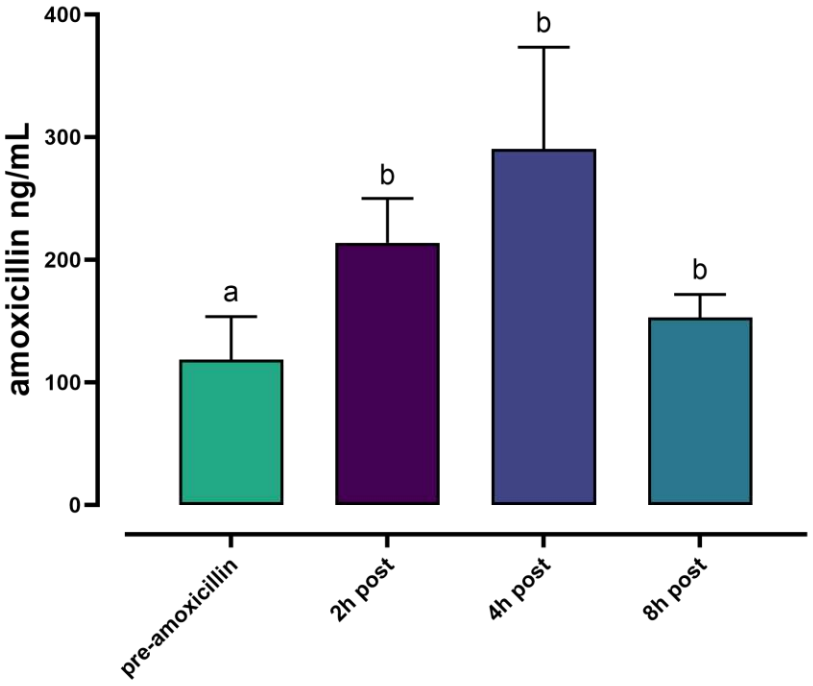
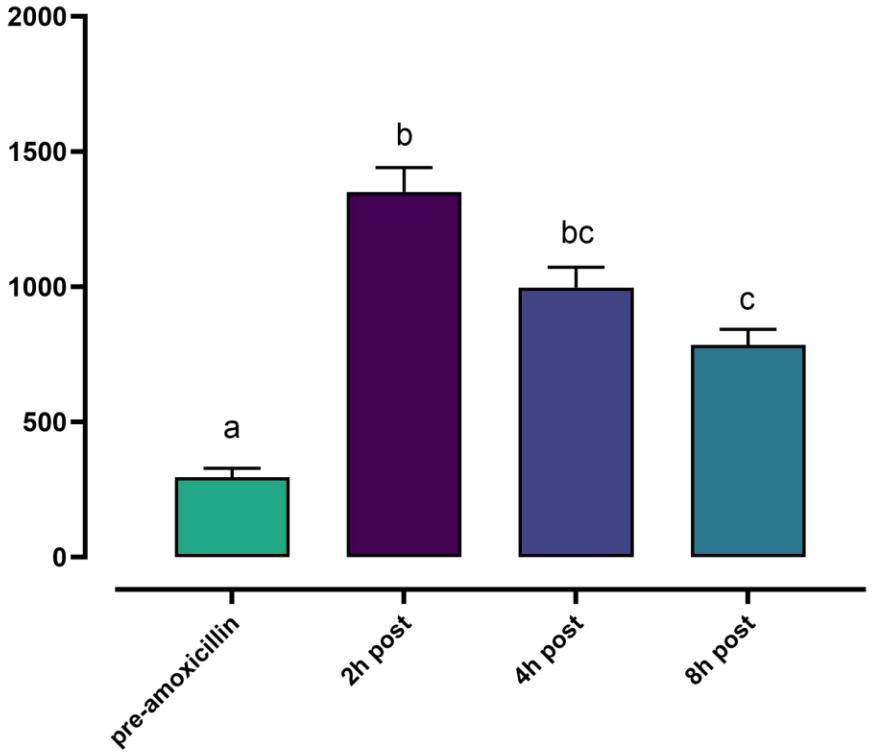
AMOXICILLIN (7 mg/kg IM, SID)

MILK



PLASMA



Amoxicillin was >LLOQ only in 6.6% of piglets plamsa samples

BioNotus BioAnalysis & Pharmacometrics

LLOQ: 10 ng/ml
ULOQ: 10000 ng/ml

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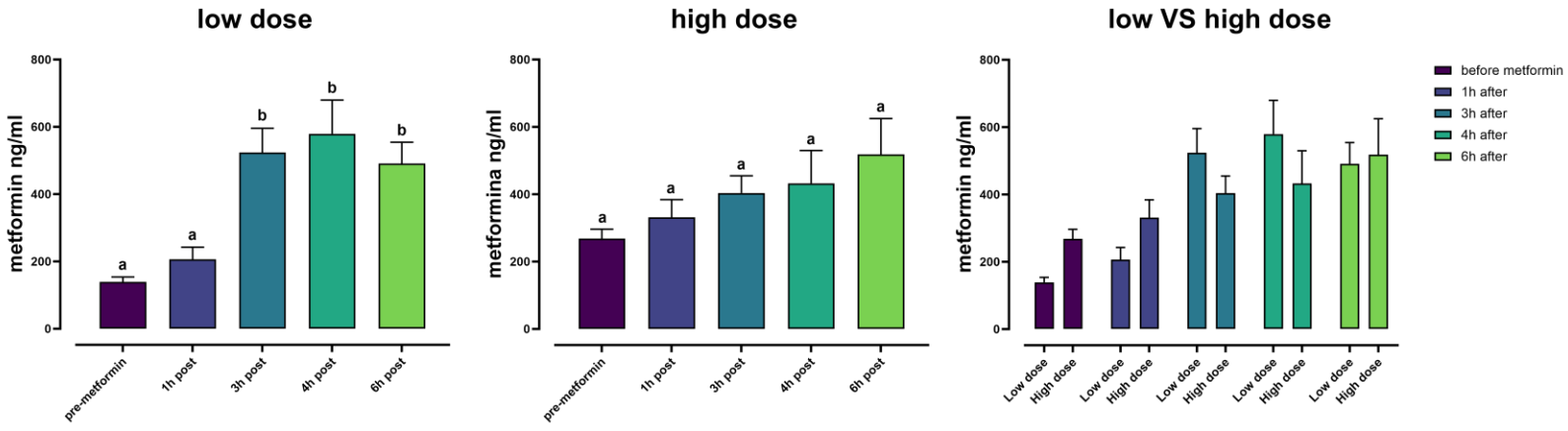
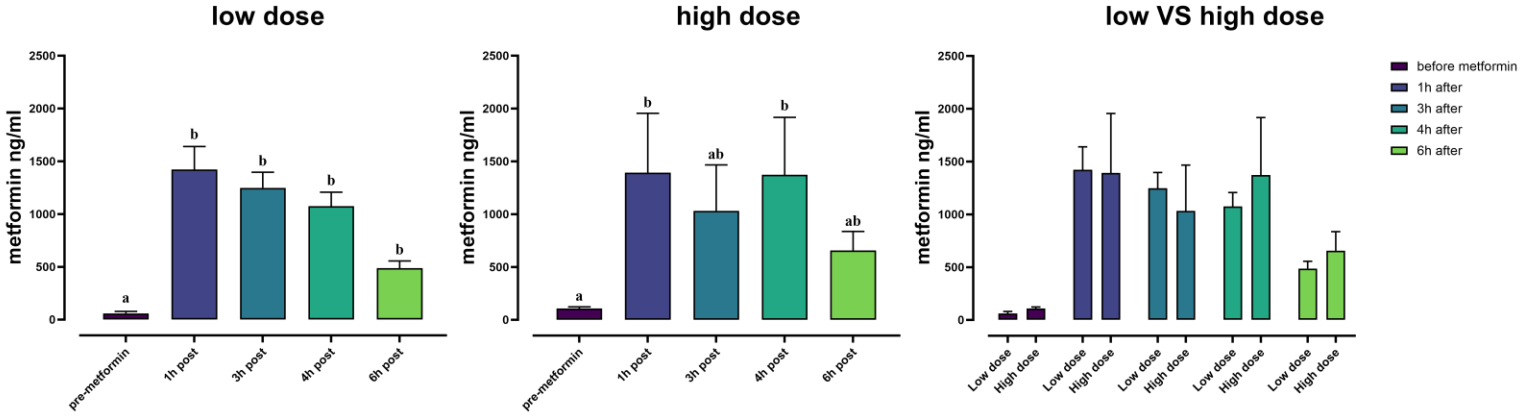
METFORMIN - Sows

SOW MILK



SOW PLASMA



Low Dose: 500 mg/day
High Dose: 850 mg/day

BioNotus BioAnalysis & Pharmacometrics

LLOQ: 2 ng/ml
ULOQ: 1600 ng/ml

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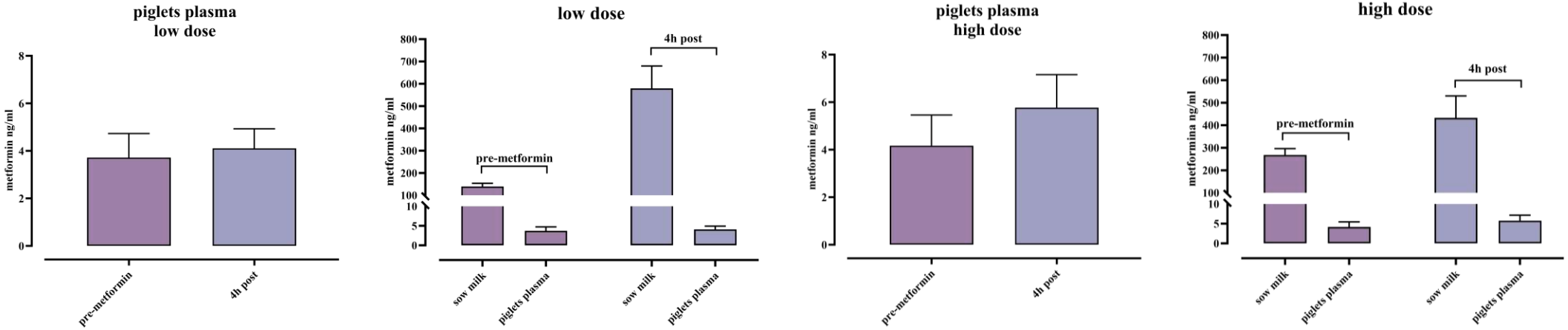
METFORMIN - Piglets



Low Dose: 500 mg/day
High Dose: 850 mg/day

BioNotus BioAnalysis & Pharmacometrics

LLOQ: 2 ng/ml
ULOQ: 1600 ng/ml

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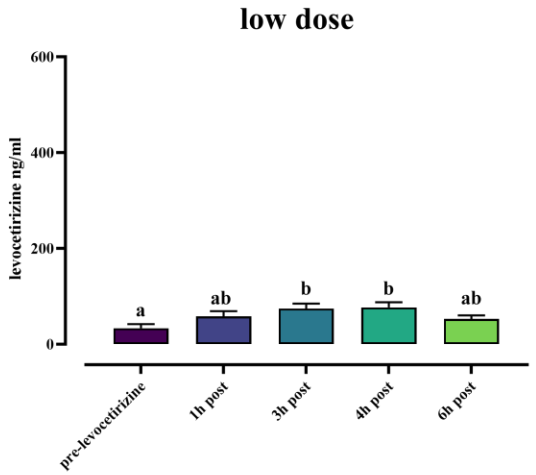
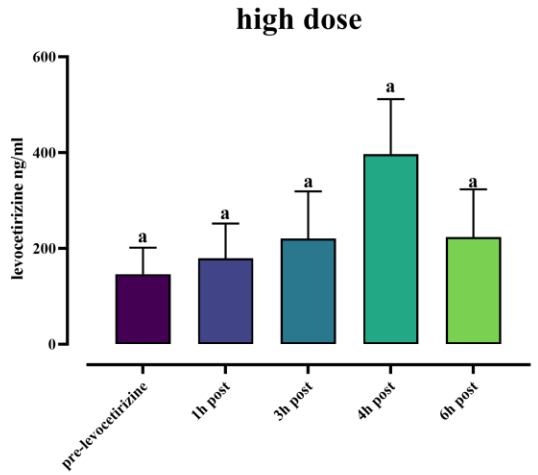
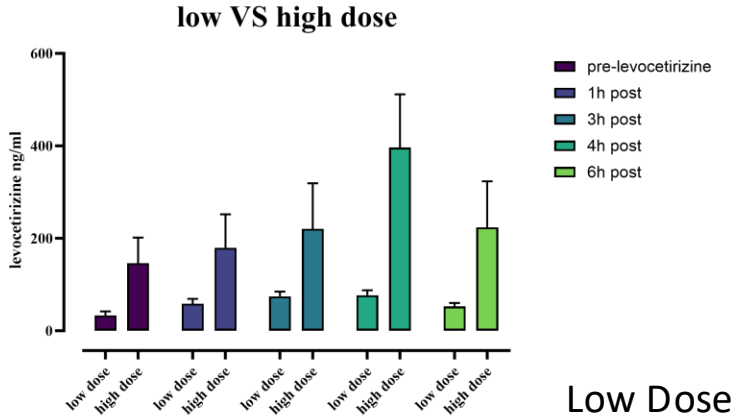
LEVOCETIRIZINE - Sows

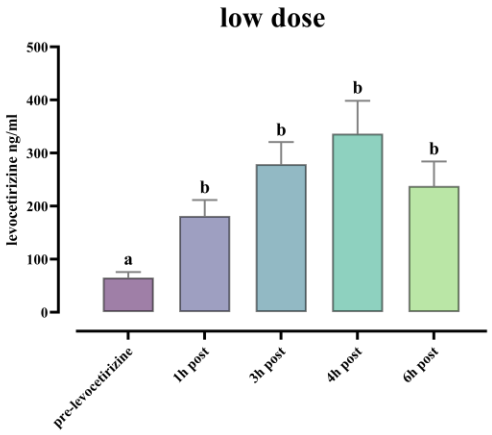
SOW MILK







SOW PLASMA



Low Dose: 15 mg/day
High Dose: 40 mg/day

BioNotus
BioAnalysis &
Pharmacometrics

LLOQ: 1 ng/ml
ULOQ: 1000 ng/ml

efpia imi innovative medicines initiative
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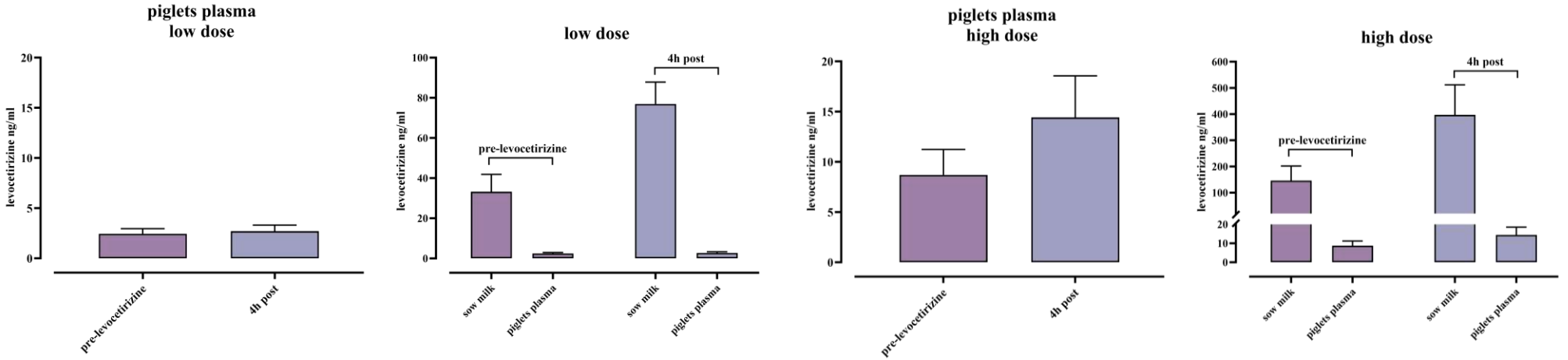
LEVOCETIRIZINE - Piglets



Low Dose: 15 mg/day
High Dose: 40 mg/day

BioNotus BioAnalysis & Pharmacometrics

LLOQ: 1 ng/ml
ULOQ: 1000 ng/ml

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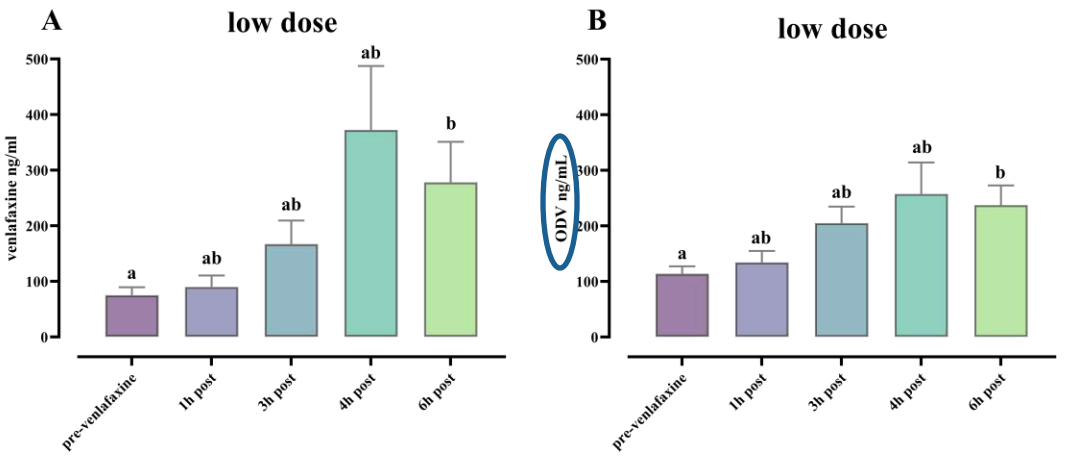
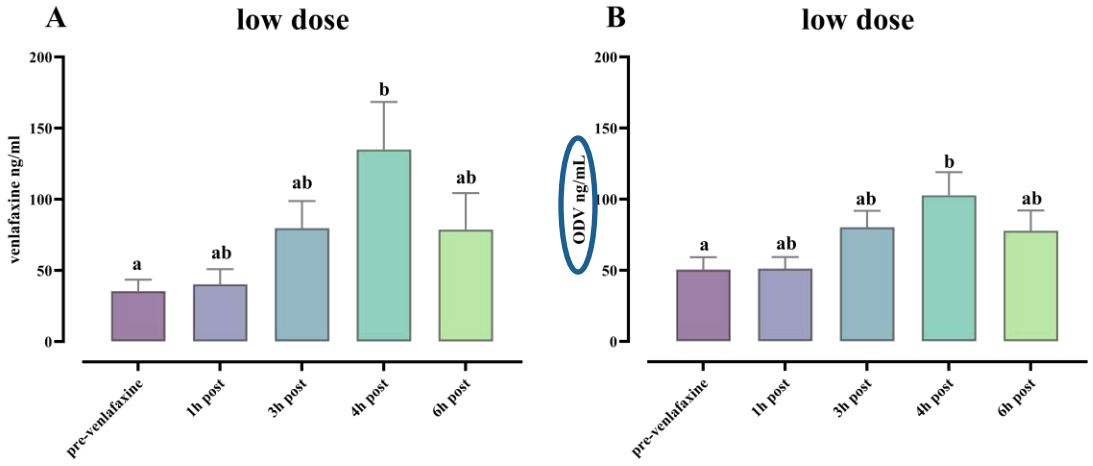
VENLAFAXINE - Sows

SOW MILK

SOW PLASMA





Low Dose: 75 mg/day
~~High Dose: 375 mg/day~~

BioNotus
BioAnalysis & Pharmacometrics

LLOQ: 0.5 ng/ml
ULOQ: 500 ng/ml

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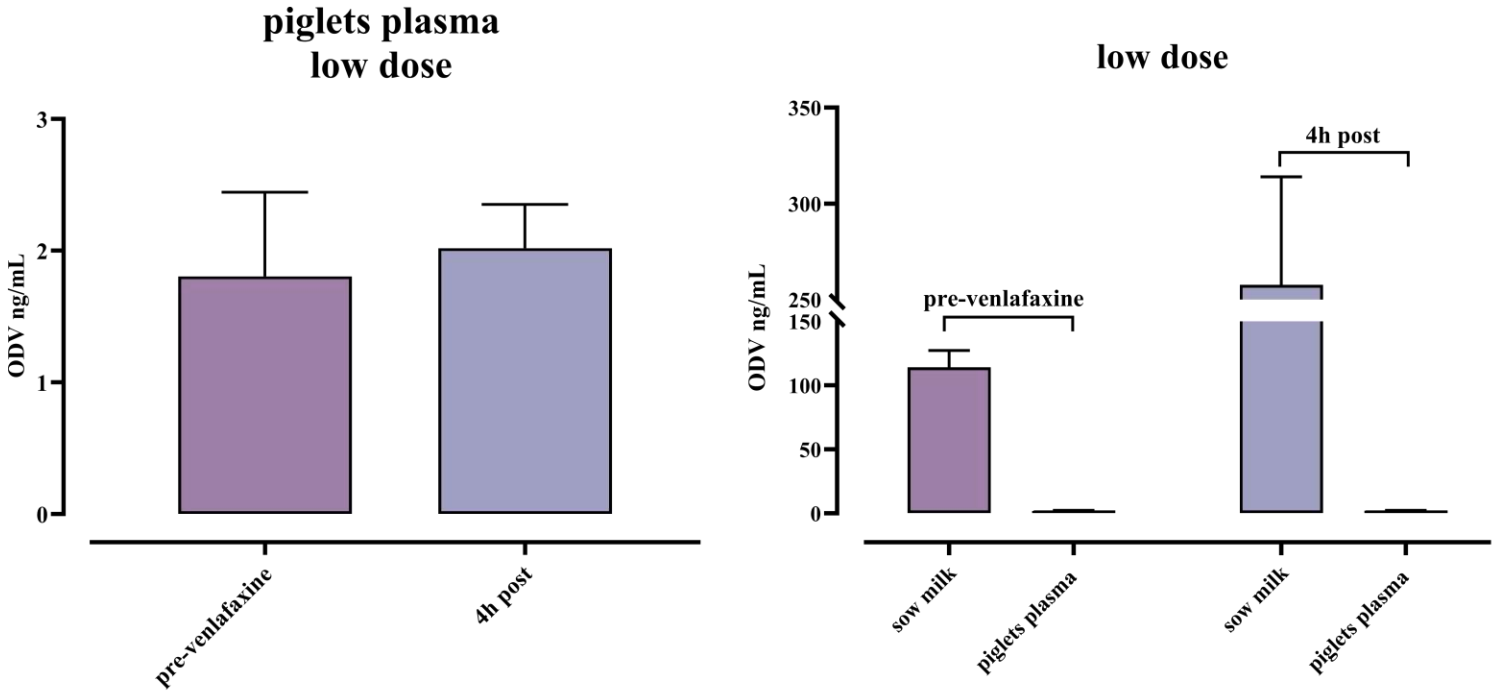
VENLAFAXINE - Piglets



Low Dose: 75 mg/day
~~High Dose: 375 mg/day~~

BioNotus
BioAnalysis &
Pharmacometrics

LLOQ: 0.5 ng/ml
ULOQ: 500 ng/ml

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MILK/PLASMA RATIOS


Medicine	Dose mg/kg	Admin route	0h	2h post	4h post	8h post	MEDIAN	HUMAN
Amoxicillin	7	IM	**0.38** ±0.05	**0.20** ±0.04	**0.35** ±0.12	**0.22** ±0.04	0.16	0.04-0.06

Medicine	Dose mg/day	Admin route	0h	1h post	3h post	4h post	6h post	MEDIAN	HUMAN
Metformin	500	OS	**3.52** ±0.38	**0.17** ±0.03	**0.43** ±0.05	**0.58** ±0.10	**1.16** ±0.14	0.69	0.13-1.00
Metformin	800	OS	**2.59** ±0.24	**0.64** ±0.29	**0.73** ±0.20	**0.38** ±0.06	**1.13** ±0.30	0.72	
Levocetirizine	15	OS	**0.31** ±0.04	0.30 ±0.02	**0.28** ±0.02	**0.21** ±0.02	**0.23** ±0.02	0.26	0.20
Levocetirizine	40	OS	**0.66** ±0.25	**0.32***	**0.24***	**NA**	**0.30***	0.36	
Venlafaxine	75	OS	**2.96** ±0.40	**2.83** ±0.33	**2.83** ±0.31	**2.92** ±0.69	**3.99** ±0.77	2.55	2.23
ODV			**2.54** ±0.21	**2.64** ±0.24	**2.79** ±0.31	**2.54** ±0.48	**3.45** ±0.41	2.50	NA
Venlafaxine	375	OS	**2.58** ±0.37	**2.47** ±0.22	**2.06** ±0.10	**2.49** ±0.25	**2.12** ±0.15	2.21	2.23
ODV			**2.85** ±0.42	**2.30** ±0.14	**2.12** ±0.23	**2.85** ±0.51	**2.19** ±0.18	2.21	NA

M/P ratio are expressed as mean ±SEM; *= only 1 observation available

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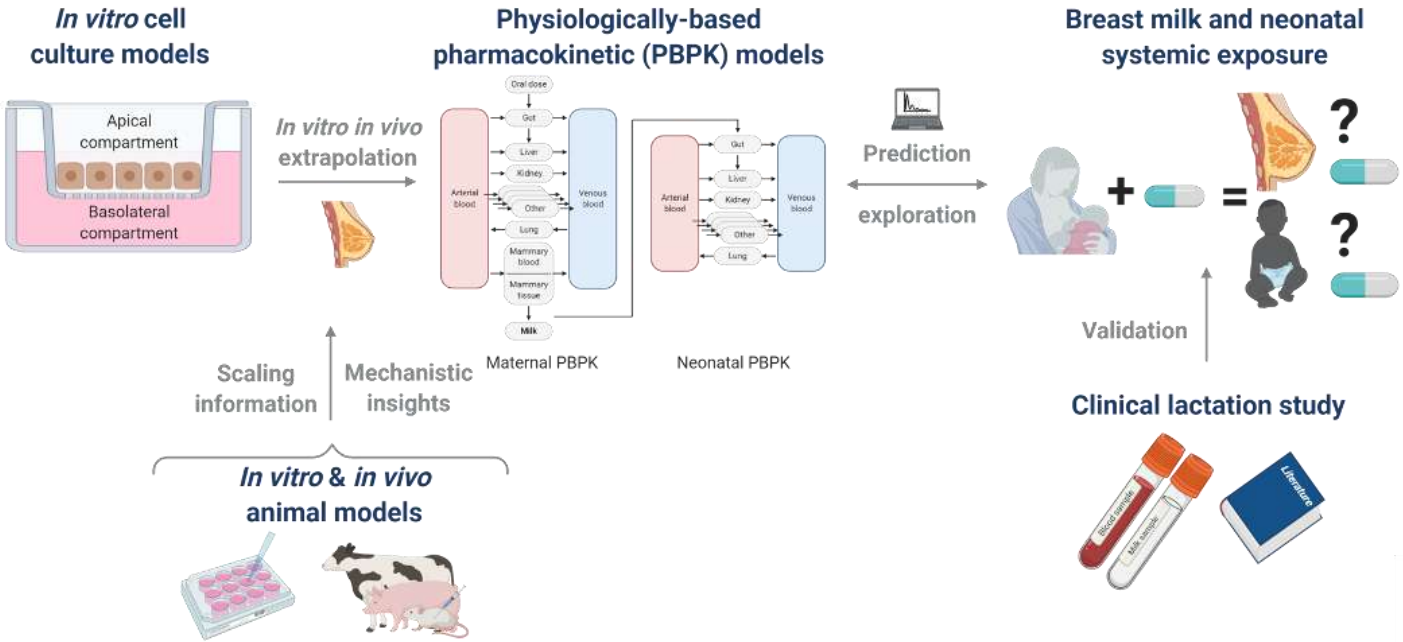
Not only in vivo….



animals

MDPI

Article

Development of a Pig Mammary Epithelial Cell Culture Model as a Non-Clinical Tool for Studying Epithelial Barrier—A Contribution from the IMI-ConcePTION Project

Chiara Bernardini [1], Debora La Mantia [1], Roberta Salaroli [1], Augusta Zannoni [1,2,*], Nina Nauwelaerts [3], Neel Deferm [3], Domenico Ventrella [1], Maria Laura Bacci [1], Giuseppe Sarli [1], Michele Bouisset-Leonard [4], Pieter Annaert [3] and Monica Forni [1,2]

Biomedicine & Pharmacotherapy 136 (2021) 111038

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

A comprehensive review on non-clinical methods to study transfer of medication into breast milk – A contribution from the ConcePTION project

Nina Nauwelaerts [a], Neel Deferm [a], Anne Smits [b,c], Chiara Bernardini [d], Bart Lammens [e], Peggy Gandia [f], Alice Panchaud [g,h], Hedvig Nordeng [i], Maria Laura Bacci [d], Monica Forni [d], Domenico Ventrella [d], Kristel Van Calsteren [j], Anthony DeLise [k], Isabelle Huys [l], Michele Bouisset-Leonard [m], Karel Allegaert [c,l,n], Pieter Annaert [a,*]

Research in Veterinary Science 172 (2024) 105244

Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

Isolation and characterization of mammary epithelial cells derived from Göttingen Minipigs: A comparative study *versus* hybrid pig cells from the IMI-ConcePTION Project

Chiara Bernardini [a,b], Salvatore Nesci [a], Debora La Mantia [a,*], Roberta Salaroli [a], Nina Nauwelaerts [c], Domenico Ventrella [a,b], Alberto Elmi [a], Fabiana Trombetti [a], Augusta Zannoni [a,b], Monica Forni [b,d]

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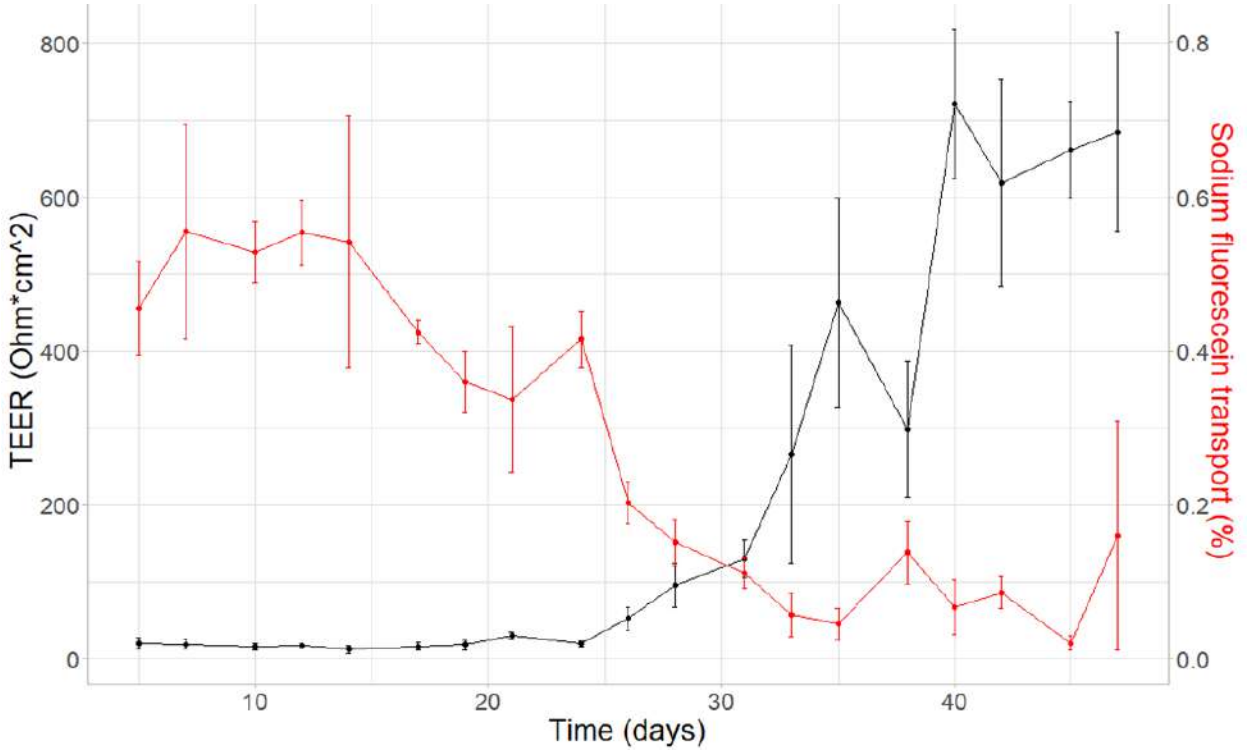
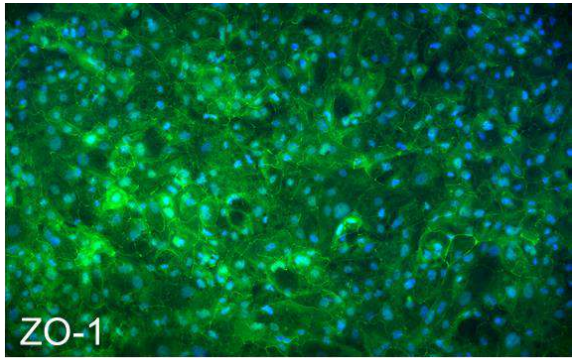
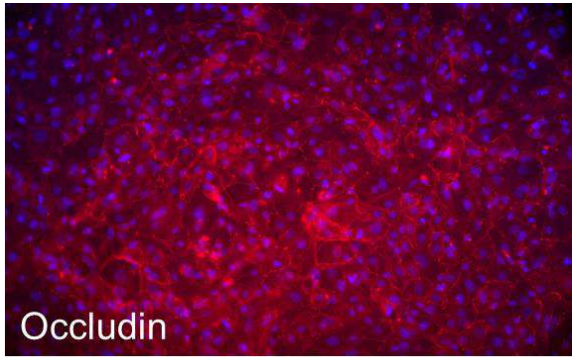
In vitro: hMECs

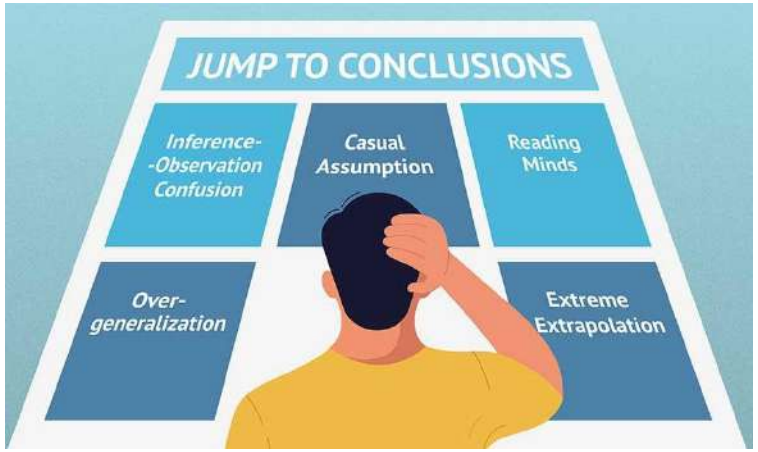
- Culture protocol was established using primary human Mammary Epithelial Cells
- Epithelial cell phenotype was confirmed
- hMECs form a tight barrier around 35 days of culture on inserts
- Drug transporter proteins (uptake/efflux) have been characterized
- Paper in preparation: human mammary epithelial cells (hMECs) culture model for the blood milk barrier. A Contribution from the ConcePTION Project







Conclusions



- The study design led to high definition results in terms of M/P ratio
- Animals well tolerated all procedures and were cooperative
- The model can be refined by better rationalizing piglets samplings
- A wider variety of medicines needs to be tested to assess applicability of the trial
- Can this be a feasible and sustainable trial in the pharma setting?

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