# Holistic qualification of mechanistic models in drug development

Ibrahim Ince[1], **Jan Schlender**[2], Jörg Lippert[3], Rolf Burghaus[3]

1) Global Clinical Pharmacology, Boehringer Ingelheim

2) Biomedical Research, Novartis

3) Model-Informed Drug Development, Bayer

# Disclosures

The authors are Modelling & Simulation scientists overseeing mechanistic modelling activities in their respective companies.

They are active contributors to Open Systems Pharmacology but have **no personal financial interest in any Modelling & Simulation platform**.

# *Scope of presentation*

**Qualification of Individual Models in light of a given Question of Interest & Context of Use**

# Focus on adequate representation of all relevant properties of a pharmaceutical treatment

Out of scope

- Qualification of Modeling & Simulation platform
- Validation of computerized systems

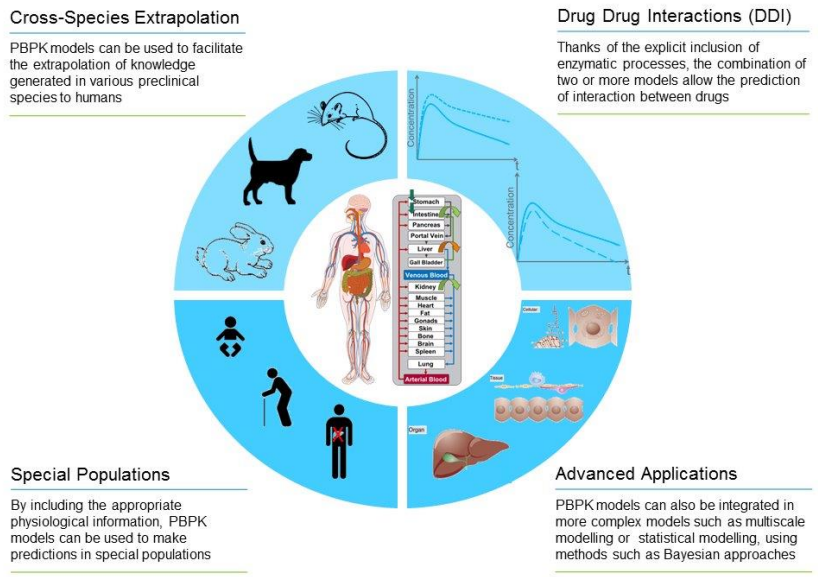
We assume availability of a qualified Modeling & Simulation platform

**In scope**

- **Scientific challenge to adequately represent all clinically relevant properties of the treatment of interest**
- **Necessity to continuously check understanding of the treatment**
- **Ability to adjust to real drugs in real development projects**

# It is practically impossible to address the diversity of challenges in Model-Informed Drug Development of real drugs with prequalified platform models

Platform design and qualification is typically focused on a limited set of commoditized standard applications.




To date, only a limited number of special cases have been qualified, primarily due to insufficient qualification data..

Kuepfer *at al.* CPT:PSP 2016

Development of real drugs continuously generates novel Questions of Interest and, so far, unseen Contexts of Use.

For any clinically relevant Question of Interest, **quantitative assessment of the consistency of scientific understanding and experimental/clinical observations** is prerequisite and important independent objective of drug development.

Mechanistic modeling if applied in a flexible, context specific fashion provides a unique opportunity for integrated assessments and learning from data.


# *# Example 1*

**Prediction of Drug-Drug-Interactions for a Typical Non-Trivial Scenario**

# PBPK-based DDI prediction is seen as a role model for platform qualification in the are of mechanistic modeling

PBPK-based frameworks for DDI prediction have been successfully qualified…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 August 2025
Doc Ref: EMADOC-1700519818-2006369
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion for Simcyp Simulator

| | |
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| Draft agreed by Scientific Advice Working Party (SAWP) | 10 April 2025 |
| Adopted by CHMP for release for consultation | 25 April 2025[1] |
| Start of public consultation | 8 May 2025[2] |
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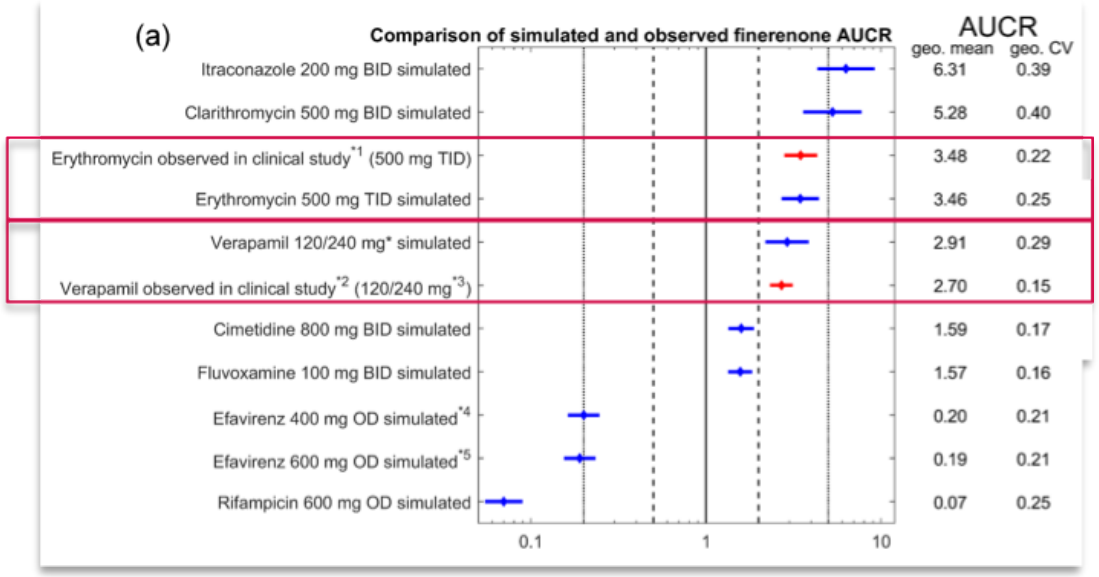
Received: 30 December 2020 | Revised: 8 March 2021 | Accepted: 1 April 2021
DOI: 10.1002/psp4.12636

ARTICLE

**A generic framework for the physiologically-based pharmacokinetic platform qualification of PK-Sim and its application to predicting cytochrome P450 3A4–mediated drug–drug interactions**

Sebastian Frechen[1] | Juri Solodenko[1] | Thomas Wendl[1] | André Dallmann[1] | Ibrahim Ince[1] | Thorsten Lehr[2] | Jörg Lippert[1] | Rolf Burghaus[1]

…and implemented in drug labelling, e.g. Finerenone



# PBPK-based DDI predictions seem to be a role model for successful application of mechanistic modeling in MIDD

PBPK-based frameworks for DDI prediction have been successfully qualified…

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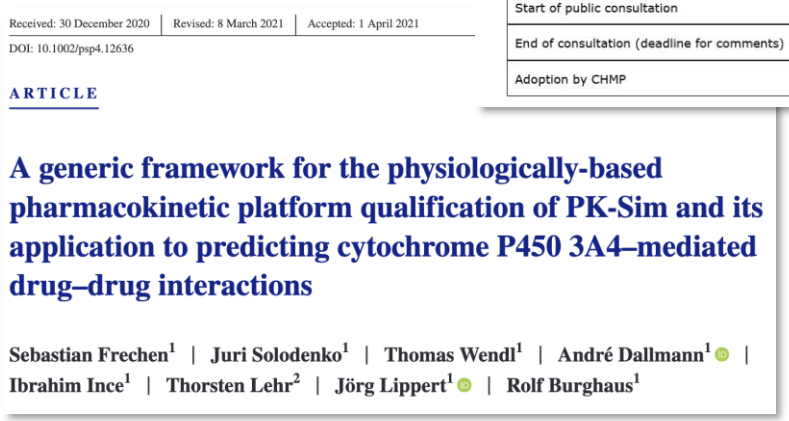

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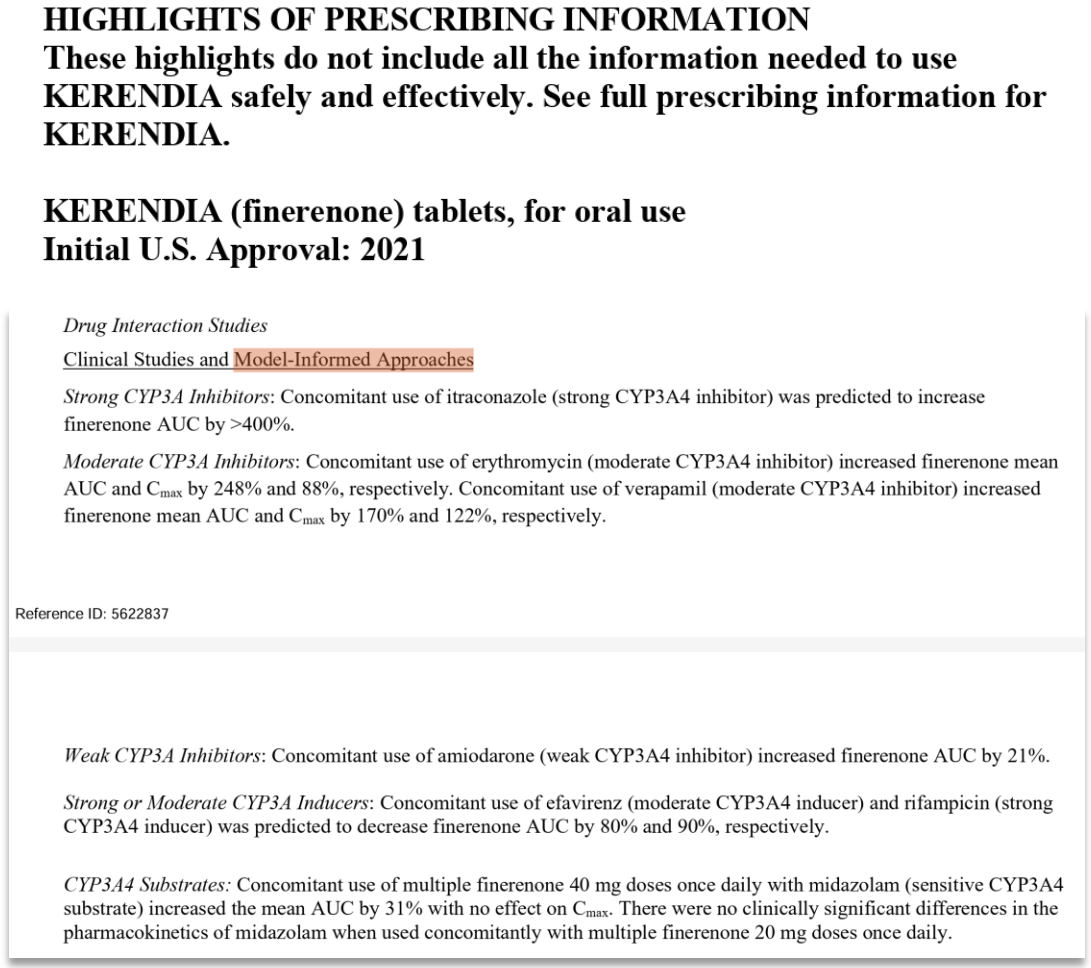


**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use KERENDIA safely and effectively. See full prescribing information for KERENDIA.**

**KERENDIA (finerenone) tablets, for oral use**
**Initial U.S. Approval: 2021**

*Drug Interaction Studies*

Clinical Studies and Model-Informed Approaches

*Strong CYP3A Inhibitors*: Concomitant use of itraconazole (strong CYP3A4 inhibitor) was predicted to increase finerenone AUC by >400%.

*Moderate CYP3A Inhibitors*: Concomitant use of erythromycin (moderate CYP3A4 inhibitor) increased finerenone mean AUC and $C_{max}$ by 248% and 88%, respectively. Concomitant use of verapamil (moderate CYP3A4 inhibitor) increased finerenone mean AUC and $C_{max}$ by 170% and 122%, respectively.

Reference ID: 5622837

*Weak CYP3A Inhibitors*: Concomitant use of amiodarone (weak CYP3A4 inhibitor) increased finerenone AUC by 21%.

*Strong or Moderate CYP3A Inducers*: Concomitant use of efavirenz (moderate CYP3A4 inducer) and rifampicin (strong CYP3A4 inducer) was predicted to decrease finerenone AUC by 80% and 90%, respectively.

*CYP3A4 Substrates:* Concomitant use of multiple finerenone 40 mg doses once daily with midazolam (sensitive CYP3A4 substrate) increased the mean AUC by 31% with no effect on $C_{max}$. There were no clinically significant differences in the pharmacokinetics of midazolam when used concomitantly with multiple finerenone 20 mg doses once daily.

# At any point in time, we need to consider the current scope of the qualification of a platform

Carbamazepine effect on Midazolam

Clinical Pharmacology & Therapeutics

Article | Open Access

**Identification of a Safe and Tolerable Carbamazepine Dosing Paradigm that Facilitates Effective Evaluation of CYP3A4 Induction**

Amita Datta-Mannan, Elaine Shanks, Eunice Yuen, Yan Jin, Jessica Rehmel, Stephen David Hall

First published: 12 June 2024 | https://doi.org/10.1002/cpt.3332

| | Observed | PBPK Platform Prediction | |
|---|---|---|---|
| | Data* | SimCYP* | PK-Sim** |
| AUCR Day 11 | 0.28 (0.24 – 0.31) | 0.24 (0.22 – 0.26) | 0.28 (CI tbd) |
| AUCR Day 14 | 0.26 (0.23 – 0.29) | 0.23 (0.21 – 0.25) | 0.26 (CI tbd) |
| $C_{max}R$ Day 11 | 0.40 (0.34 – 0.46) | 0.30 (0.28 – 0.32) | 0.42 (CI tbd) |
| $C_{max}R$ Day 14 | 0.37 (0.32 – 0.44) | 0.29 (0.27 – 0.31) | 0.41 (CI tbd) |

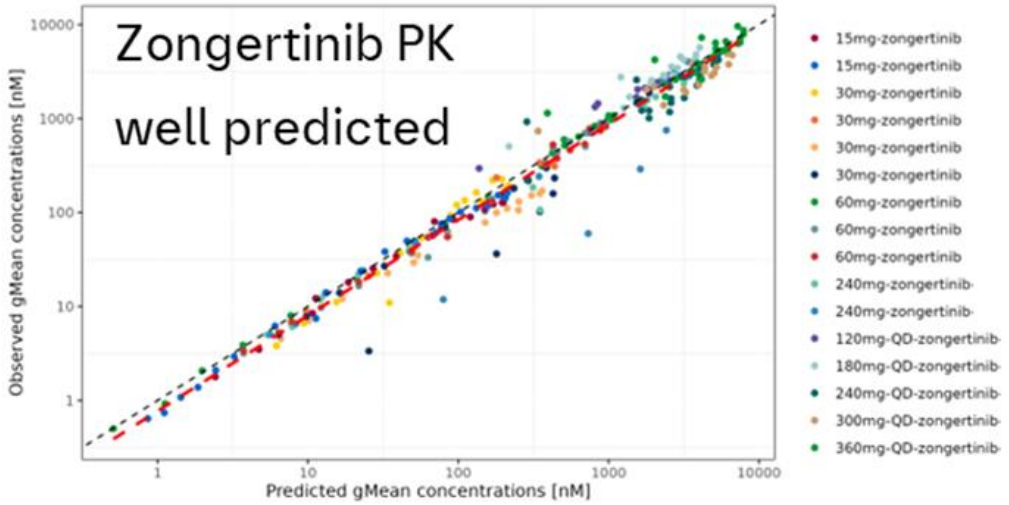
*Datta-Mannan A et al. 2024; **OSP V13 Qualification Reports

- Current versions of PBPK platforms adequately represent inducer effect of Carbamazepine on CYP3A4
- Midazolam is an ideal probe drug / victim for CYP3A4-mediated Drug-Drug Interactions
- Midazolam-Carbamazepine PK interaction can be predicted adequately

**But what about typical development candidates with more complex metabolization and excretion pathways?**

# Zongertinib – well described by PBPK model – is a substrate of CYP3A4 but also UGTs, GSTs, P-gp

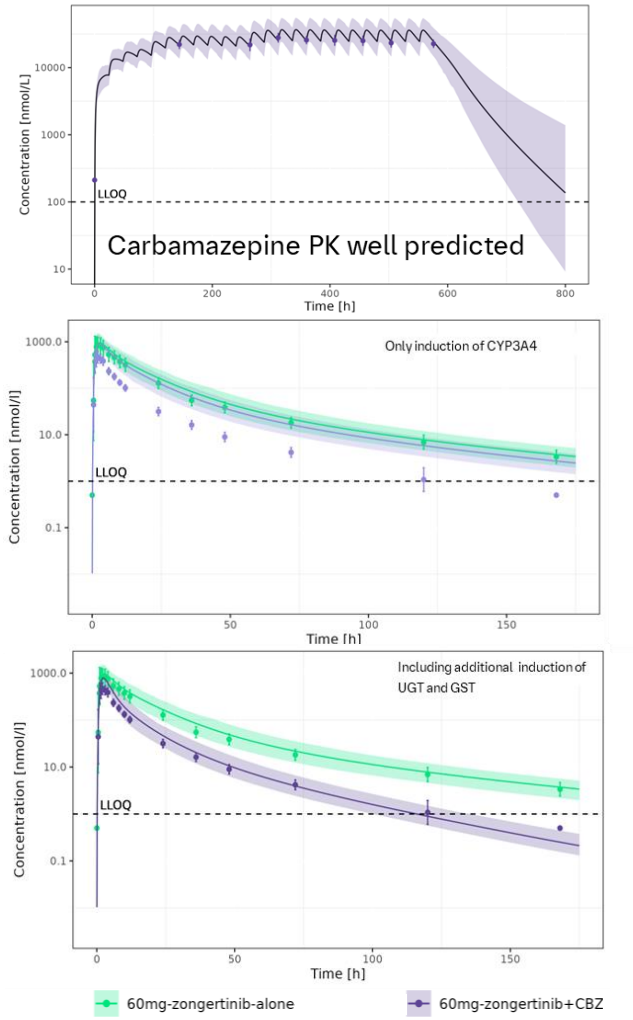
- **Zongertinib** is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing wild-type EGFR, thereby limiting associated toxicities
- **Model development goal**:
  - To improve the understanding of the pharmacokinetics (PK) behaviour and predict DDI risk with CYP3A4 inducers
- **PBPK model** successfully built using:
  - Physical chemical properties, active processes (CYP3A4, P-gp, non-specific protein binding) and clinical PK data
- **Initial DDI simulations** prior to availability of full mass-balance used carbamazepine PBPK model qualified as a CYP3A4 inducer.
- **Key Insight**: Mild impact predicted for CYP3A4 induction alone



# Since Carbamazepine is also an inducer of enzymes beyond CYP3A4 not reflected in platform models, fit-for-purpose modeling required

- **The qualified carbamazepine PBPK  model** adequately described *in vivo* data in DDI trial
- **Observed DDI with carbamazepine** stronger than predicted by CYP3A4 induction alone
- **Model refinement required** to account for additional induction effects of carbamazepine to match *in vivo* data

- **Similar deviations expected for other inducers without customization of models:**
  - **Rifampicin:** Broad induction profile, similar to carbamazepine
  - **Efavirenz:** Mixed effects – induces some pathways, inhibits others



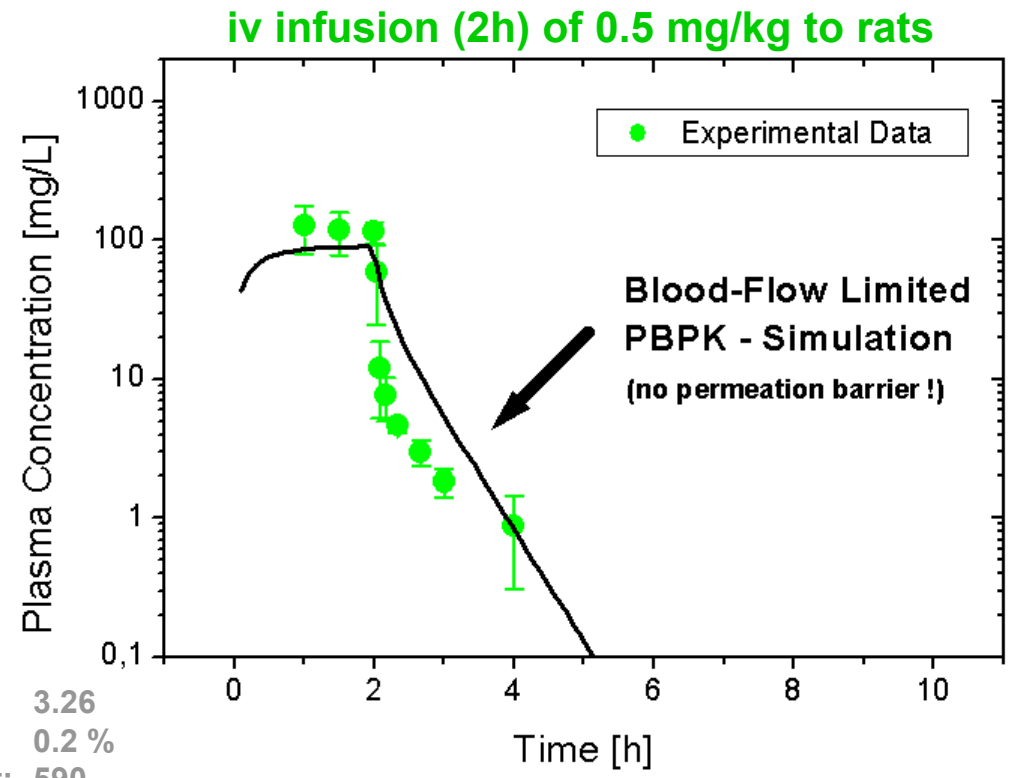

# *Example 2*

## Sequential Translation from Preclinical to Healthy Volunteers and Patients

## Learning from Data

# PBPK-modeling with default model identified an inconsistency between assumed drug profile and preclinical PK data…

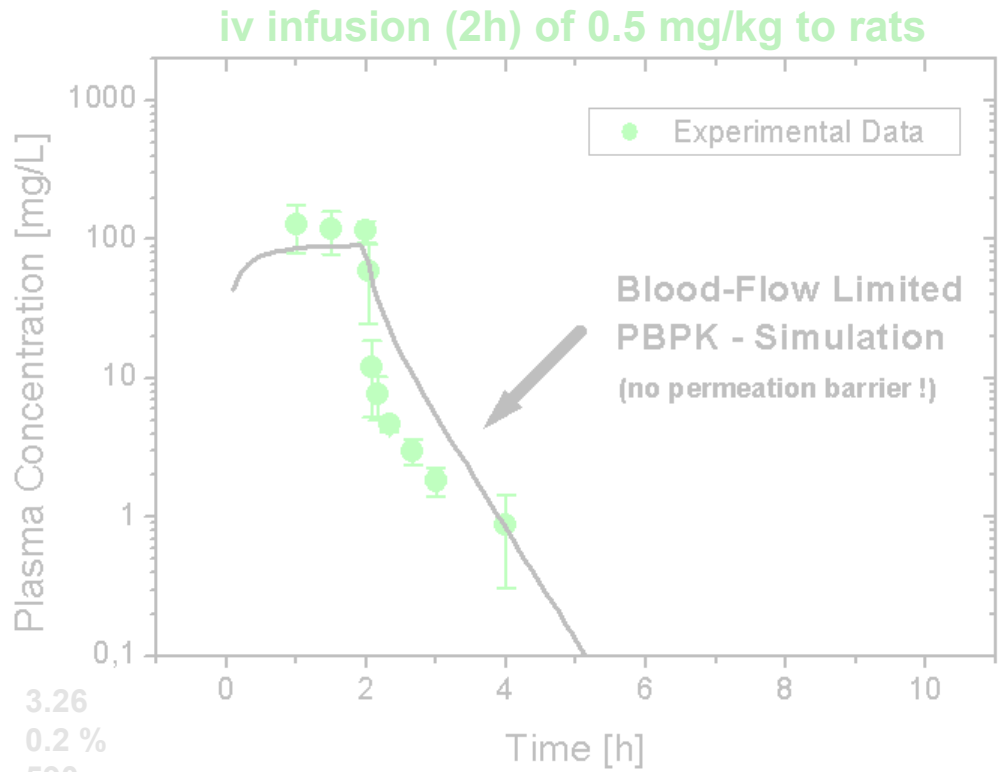
Drug candidate showed extremely high clearance inconsistent with default passive ADME represented in template PBPK models




LogMA: 3.26
Plasma fu: 0.2 %
MolWeight: 590
**blood-flow limited CL**

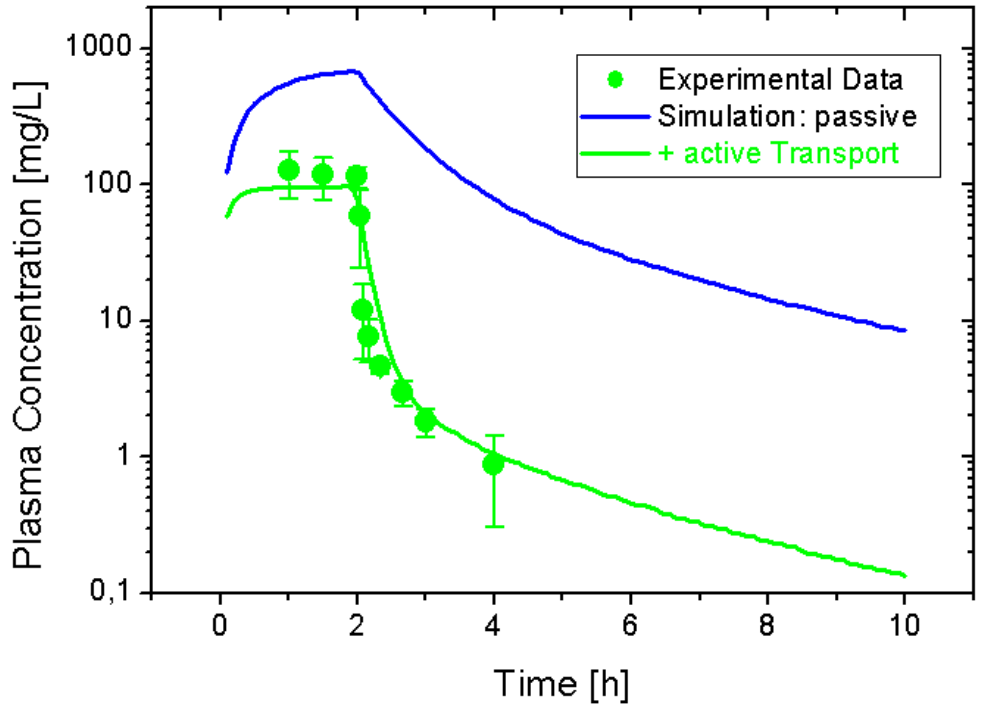
# …but also provided the mechanistic explanation for very short half-life in preclinical PK models allowing FiH extrapolation

Drug candidate showed extremely high clearance inconsistent with default passive ADME represented in template PBPK models




LogMA: 3.26
Plasma fu: 0.2 %
MolWeight: 590
blood-flow limited CL

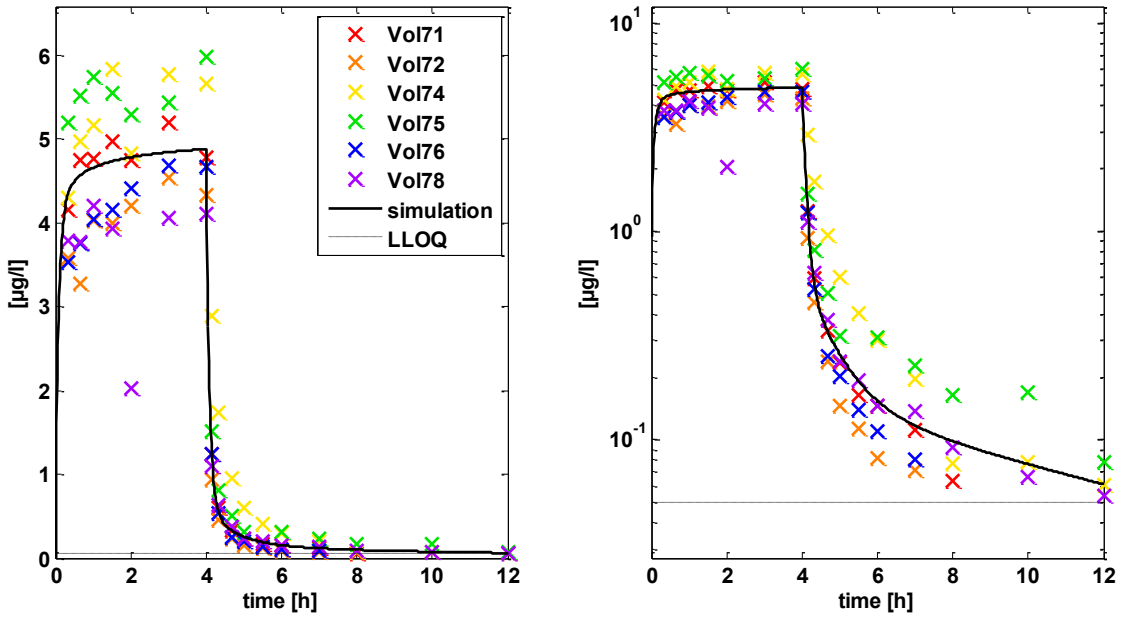
Extension of the PBPK model by liver uptake transporter triggered experimental verifcation of the OATP substrate property of the drug



# FiH data confirmed the relevance of OATP transport but measurements in humans at later time points revealed another inconsistency…

Measurements with optimized bioanalytical assay revealed longer terminal half-life which could be explained by adding target-mediated deposition of the small molecule to the PBPK model

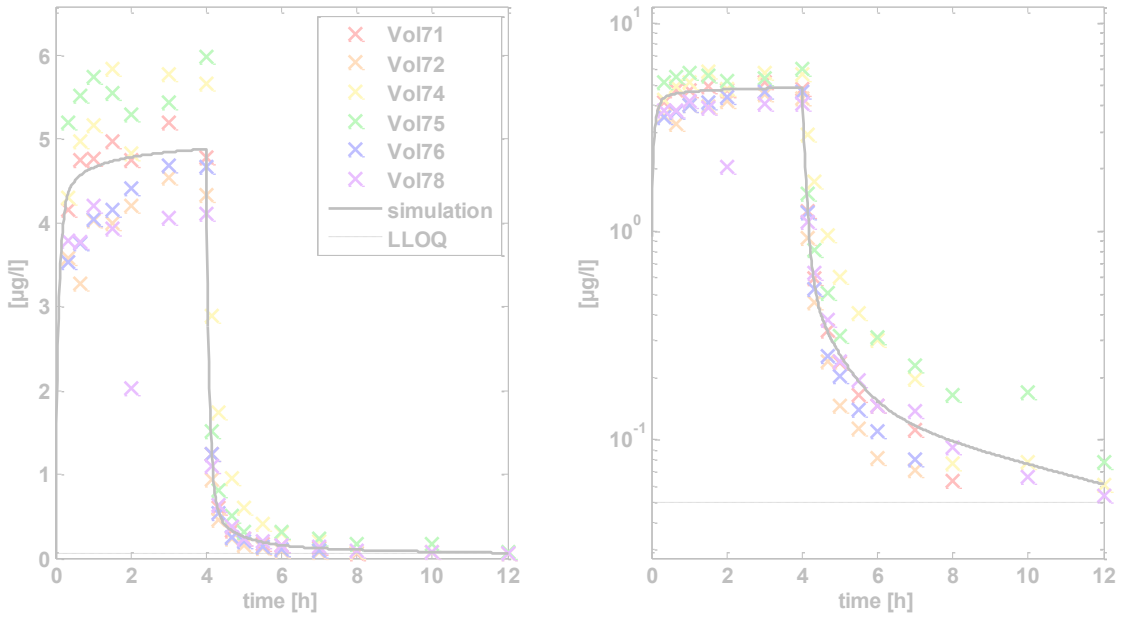
**4h iv infusion in HV**



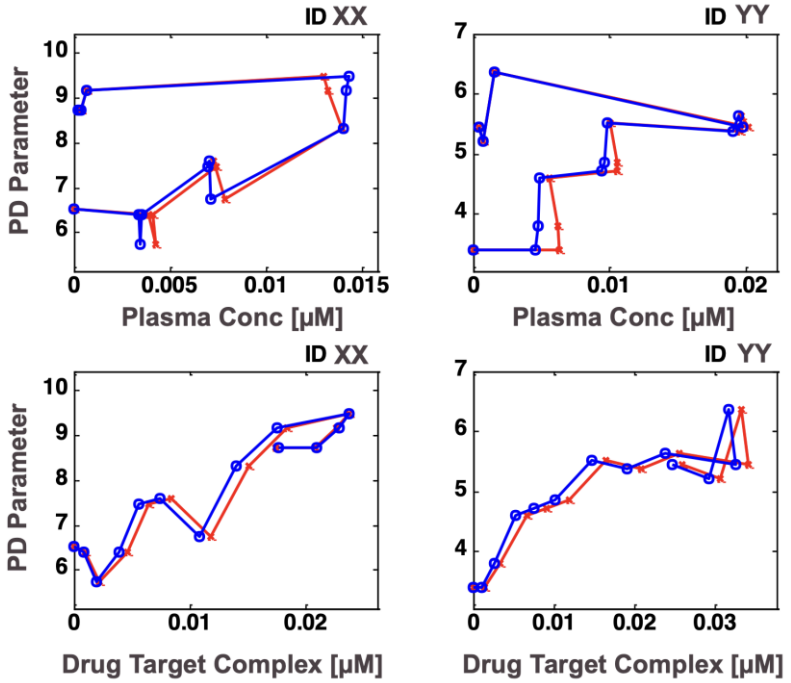
# …and Target-Mediated Disposition for this small molecule explained both terminal PK half-life and PD hysteresis

Measurements with optimized bioanalytical assay revealed longer terminal half-life which could be explained by adding target-mediated deposition of the small molecule to the PBPK model

**4h iv infusion in HV**




Time-profile of the target-drug complex predicted by the PBPK model immediately explained the observed PD hysteresis




data only

**PD vs PBPK prediction**

# Finally, the PBPK model with OATP transport and TMDD even helped to identify a pharmacodynamic feedback loop modulating PK in patients

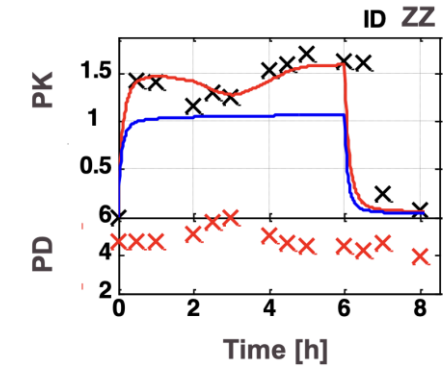
Modulations of the plasma concentration during infusion could be mechanistically explained by incorporating the PD effect on PK in the PBPK model

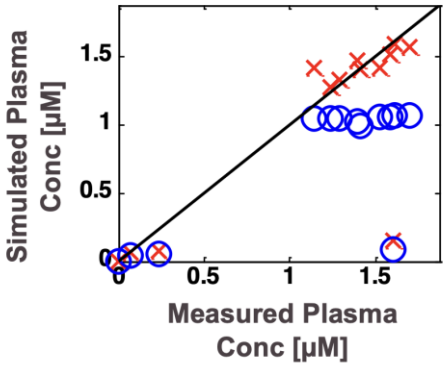
-- PBPK Simulation w/o PD effect

-- PBPK Simulation with PD effect

oo PBPK Simulation w/o PD effect

xx PBPK Simulation with PD effect

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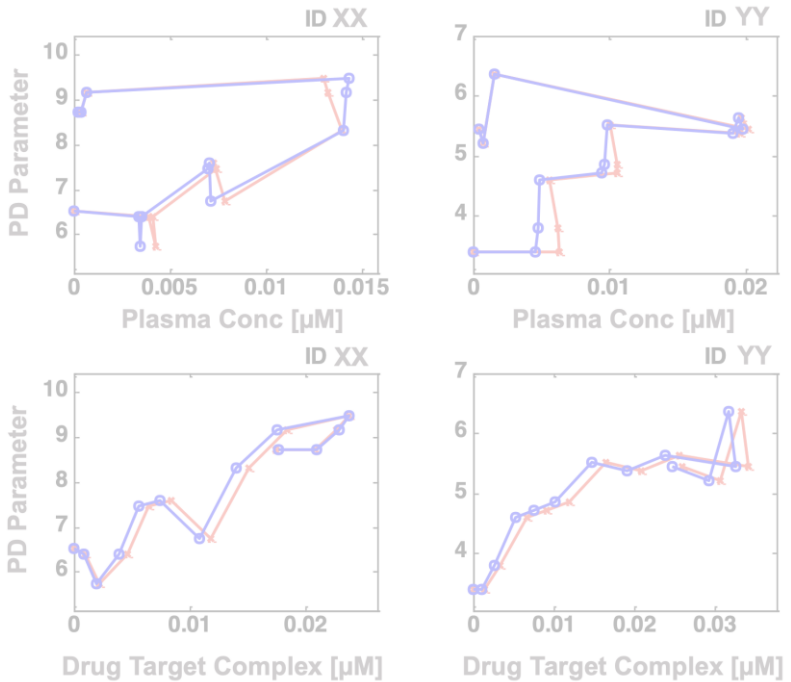



data only

**PD vs PBPK prediction**

NOVARTIS

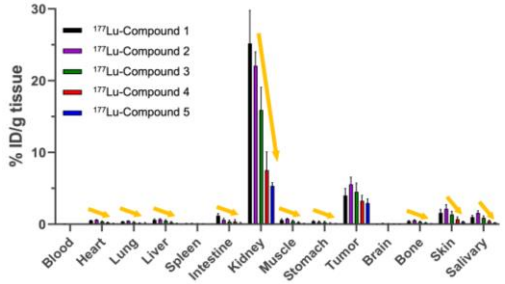
# *Example 3*

## Prediction of Effect of Renal Impairment on Tissue Exposure

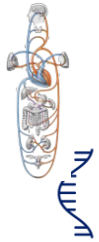
# For radioligand-targeting constructs, tissue exposure is a decisive outcome, but it is driven by target & disease specifics usually not covered by platform qualification

## Inputs

**Observed** BioD




**Species-specific:**

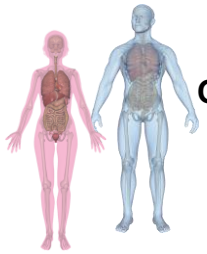


Source: Data on file.[1]

**Physiology**

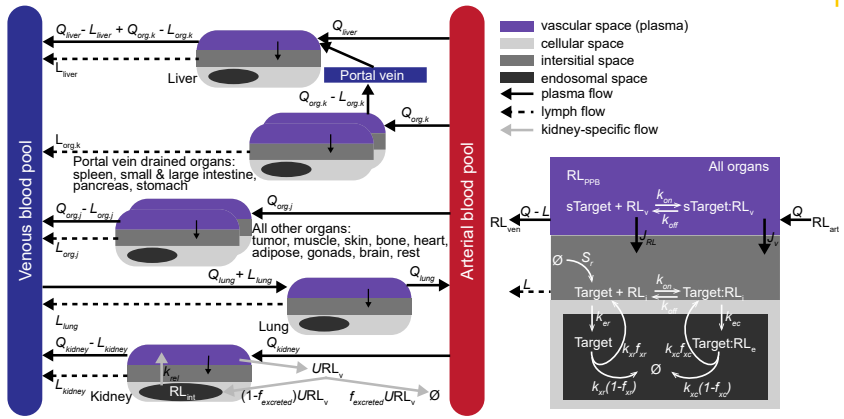
**Target expression profiles**

**Compound properties (e.g., affinity, PPB, stability, …)**



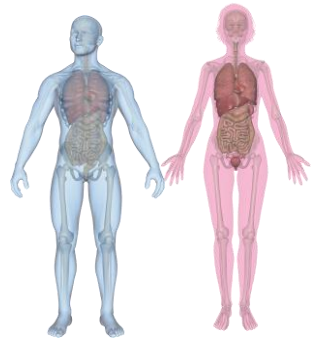
**Observed** BioD in clinic for another compound to same target

## PBPK-based Exposure prediction




- Fit mouse bioD → Translate organ target levels & compound properties → Simulate human bioD
- Fit human bioD → Adapt new compound properties → Simulate human bioD

## Outputs



**Predicted** human BioD and **absorbed doses**

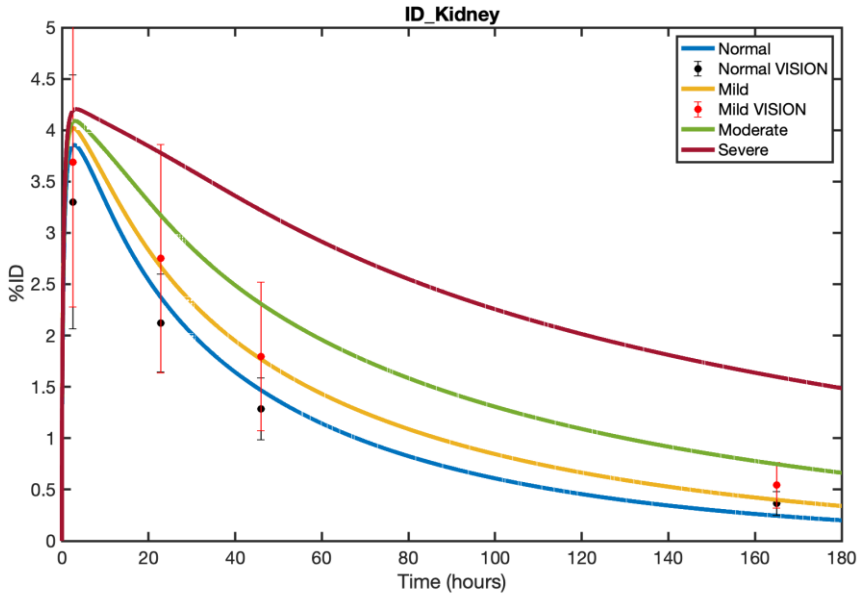
**OLINDA/EXM®**

Gaudet S. 4th RPT Summit, July 29, 2025, San Diego CA

EMA HMA Heads of Medicines Agencies

# To justify [$^{177}$Lu]Lu-PSMA-617 dosage for patients with moderate or severe renal impairment PBPK model had to be customized and trained with image-data

1. Fit to data from patients with normal kidney function
2. Validate predictive simulation against data from patients with mild impairment
3. Extrapolate to moderate and severe impairment




Clinical Pharmacology & Therapeutics

Article | Open Access

**Current Use of Physiologically Based Pharmacokinetic modeling in New Medicinal Product Approvals at EMA**

Polly Paul, Pieter J. Colin, Flora Musuamba Tshinanu, Carolien Versantvoort, Efthymios Manolis, Kevin Blake

First published: 02 January 2025 | https://doi.org/10.1002/cpt.3525 | Citations: 9

**Table 1.** Proposed intended uses and outcomes of assessments of PBPK models in approved MAAs in 2022 and 2023

| INN | Intended use(s) | Qualified or otherwise | Reason(s) for non-qualification (where applicable) |
|---|---|---|---|
| Lutetium (177Lu) vipivotide tetraxetan | Renal impairment | Qualified | |

| | |
|---|---|
| Lutetium (177lu) vipivotide tetraxetan EPAR | Adjusted dosing for patients with renal impairment was not proposed, instead a new PBPK model was used to predict exposure in patients with renal impairment. Kidney dose at cycle 6 was increased more than twofold in patients with moderate renal impairment and 1,7-fold in patient with mild renal impairment according to the VISON study and the proposed PBPK model. |

Gaudet S. 4th RPT Summit, July 29, 2025, San Diego CA
Herrmann K *et al. J Nucl Med.* 2024
Paul P et al. *Clin. Pharmacol. Ther.* 2025

EMA HMA Heads of Medicines Agencies

# *Conclusions*

**Necessity of Adequate Mechanistic Representations and Dedicated Qualification for Question of Interest**

# Conclusions

- Qualified modelling platforms
  - are of high relevance for commoditized standard applications
  - facilitate efficient M&S execution and review
- For prominent examples, Return-on-Invest (RoI) for platform qualifications is debatable
- Platform qualification alone cannot be the answer to the diversity of clinical development and regulatory challenges
- For most clinical applications, mechanistic models need to be customized and adjusted to the specific properties of the treatment of interest
- This is even more obvious for QSP models where disease biology is meant to be represented

- Mechanistic modelling is a scientific activity that requires not only deductive but also inductive generation of insights
- Computational platforms need to provide the flexibility to represent the properties of the treatment of interest
- Qualification needs to be conceptualized in the context of a specific Question of Interest and Context of Use
- Very often the specifics of the Question of Interest prevent reliance on historic reference cases and Platform Qualification can only play a supportive role

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Jinju Guk

# Thank you

jan-frederik.schlender@novartis.com

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