Prediction of dosing, schedule and drug-drug interactions of long acting agents

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Disclosure

- Research grant: ViiV and Janssen
- Consulting: AZ, Nevakar and Merck

Overview

- Drivers/mechanisms of long acting pharmacokinetics

- Modelling and simulation of drug-drug interactions

- Prediction of relevant clinical scenarios

- Design of novel formulations

- Future developments and perspectives

Long-acting ADME

Oral

Long acting

Absorption

First pass effect → Volume of distribution

Metabolism and Elimination

Absorption

Volume of distribution

Metabolism and Elimination
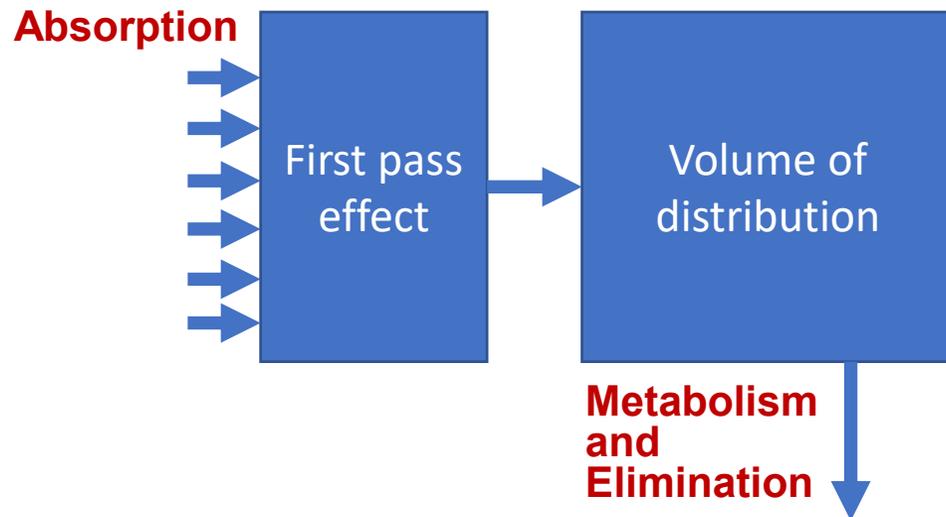
Absorption > Elimination
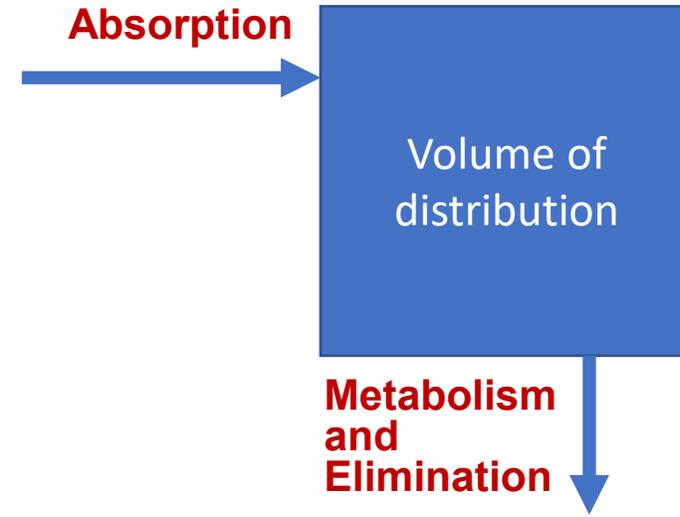
Absorption < < Elimination

Flip-flop kinetics refers to when the rate of absorption of a compound is significantly slower than its rate of elimination from the body. Therefore, the compound's persistence in the body becomes dependent on absorption rather than elimination processes.

Long acting ADME - Increased clearance

Oral

Long-acting

Absorption > Elimination
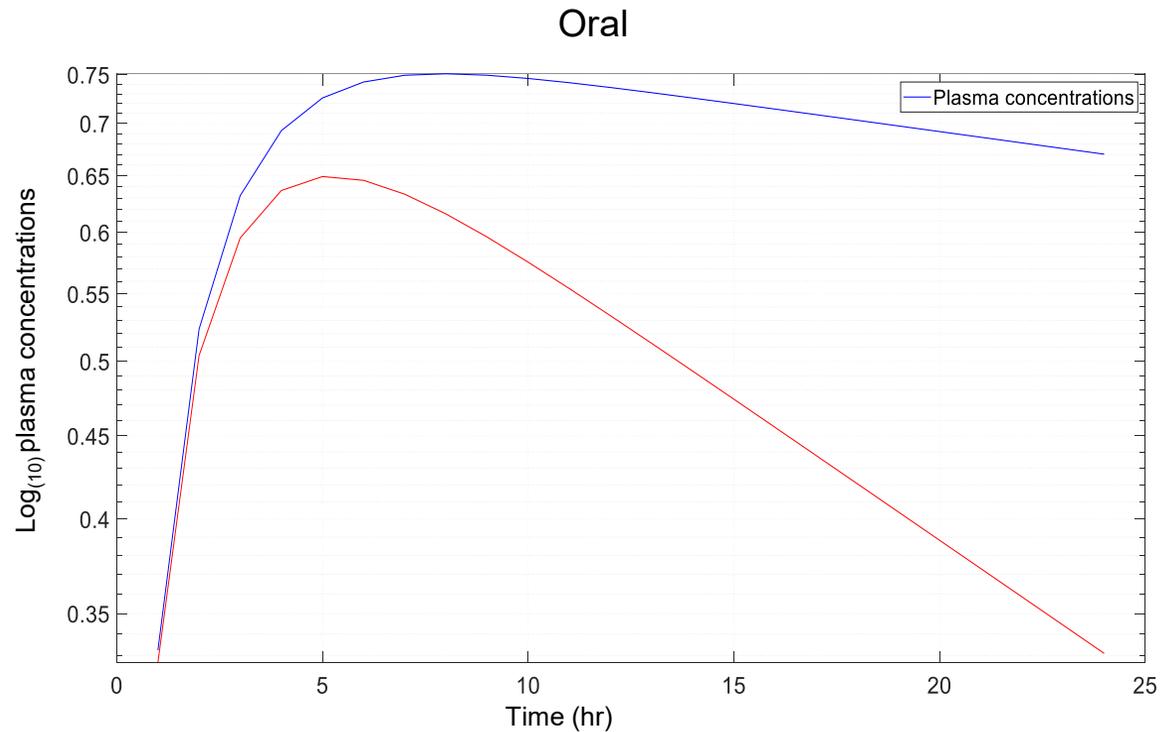
Absorption < < Elimination

Changes in clearance result in different half-life and concentrations

Changes in clearance result in similar half-life but different concentrations

Long acting ADME - Increased release
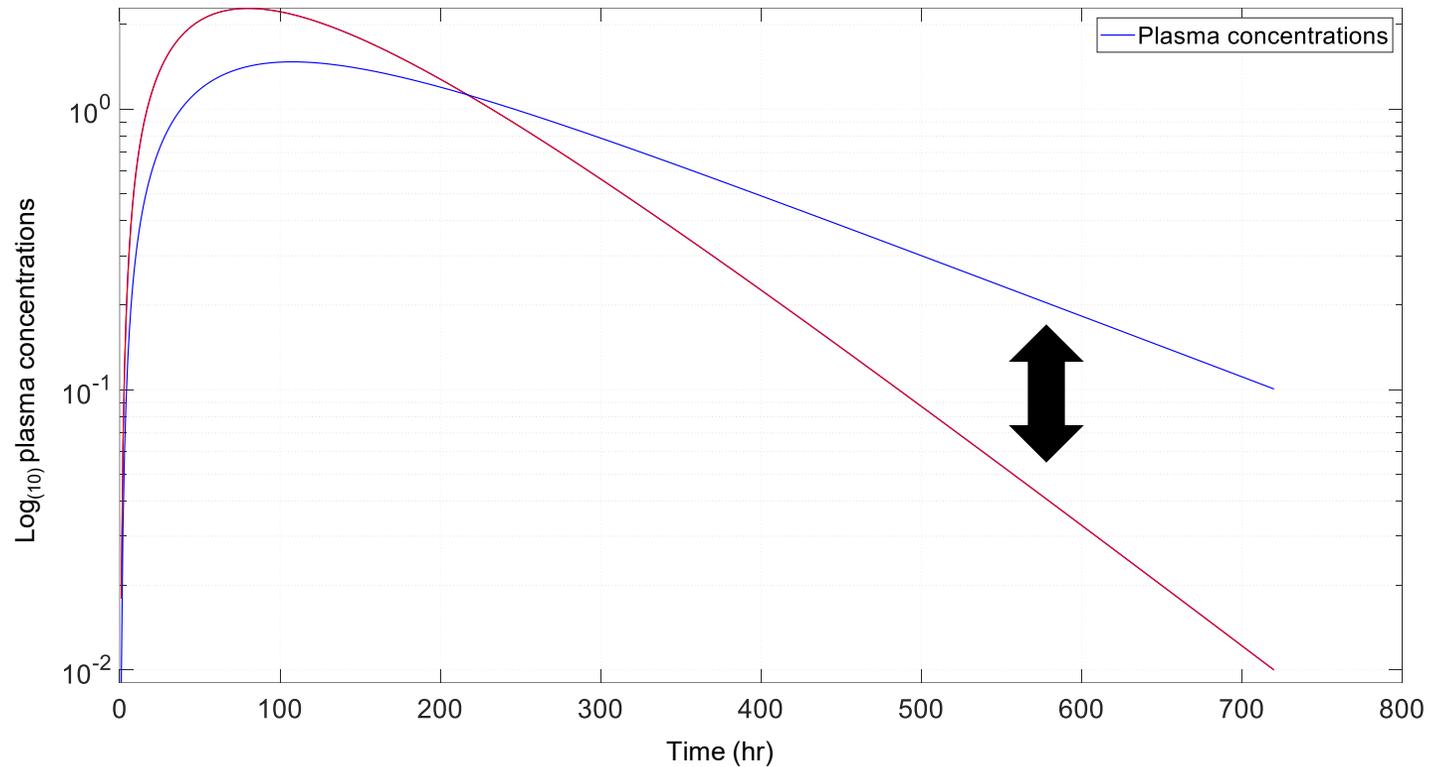
Absorption < < Elimination

Changes in absorption release result in
different half-life and concentrations
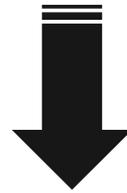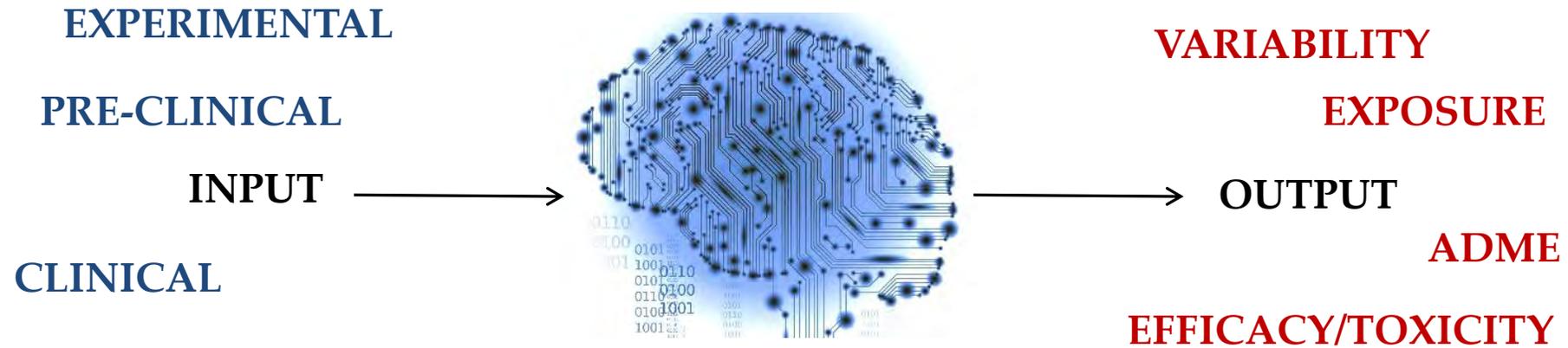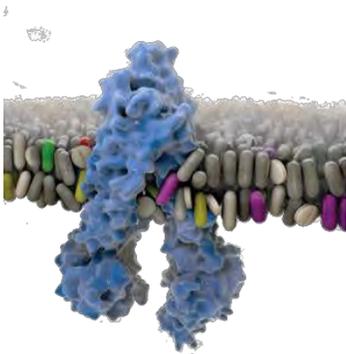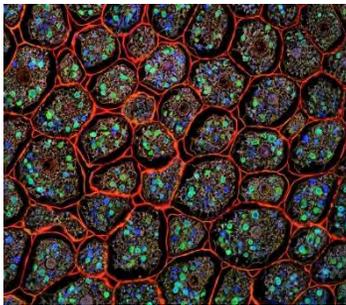
Patients

Volunteers

Transgenic animals

Animals

Tissue/Cells

Subcellular fractions

Proteins

RELEVANCE

MECHANISMS

RELEVANCE

Patients

Volunteers

Transgenic animals

Animals

Tissue/Cells

Subcellular fractions

Proteins
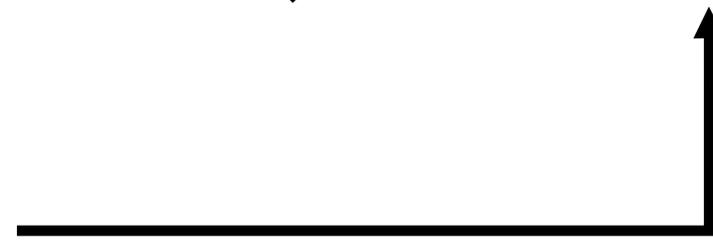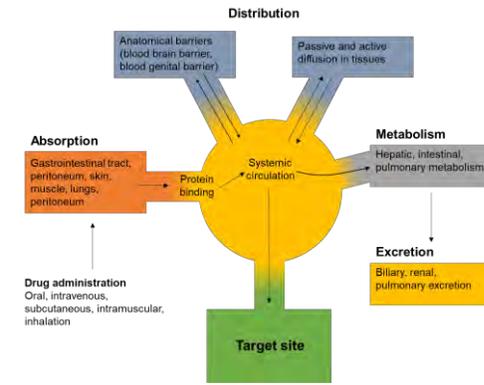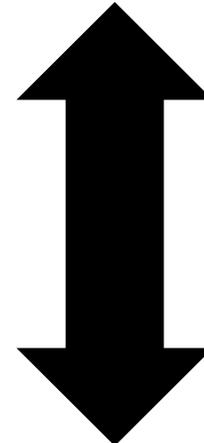
MECHANISMS

Model development and application
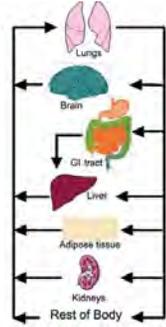
MATHEMATICAL FRAMEWORK

MODEL QUALIFICATION

CLINICAL APPLICATIONS

01

02

03

04

05

06

DMPK

MODEL TEST

PREDICTIONS

| R&D Lead selection | Preclinical | Clinical | Launch | Post-licensing |
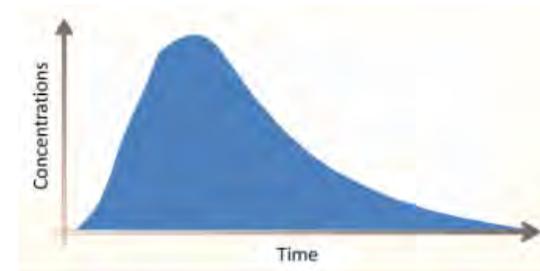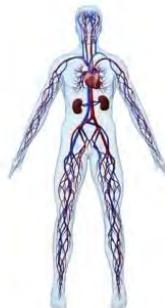
Understanding of drug disposition

- ADME process
- Tissue penetration
- Preclinical PK

Human pharmacokinetics and pharmacodynamics

- Bioavailability, clearance
- Exposure/response relationship

Optimisation of patient management

- Drug-drug interaction
- Special populations
- Pharmacogenetics

SELECTION OF OPTIMAL CANDIDATE

HUMAN DOSE PREDICTION

SIMULATION OF CLINICAL SCENARIOS

Role of pharmacokinetic modelling in the development of long-acting

Integrated strategy for the prediction of DDIs

Drug-drug interaction for LA

Oral   **Long acting**

FIRST PASS
METABOLISM   ✗

SYSTEMIC
CLEARANCE   ✗   ✗

Half-life   Absolute
                    concentrations

Oral cabotegravir

Rifampin decreased the cabotegravir **AUC by 59% and half-life by 57%** (Ford et al. 2017)
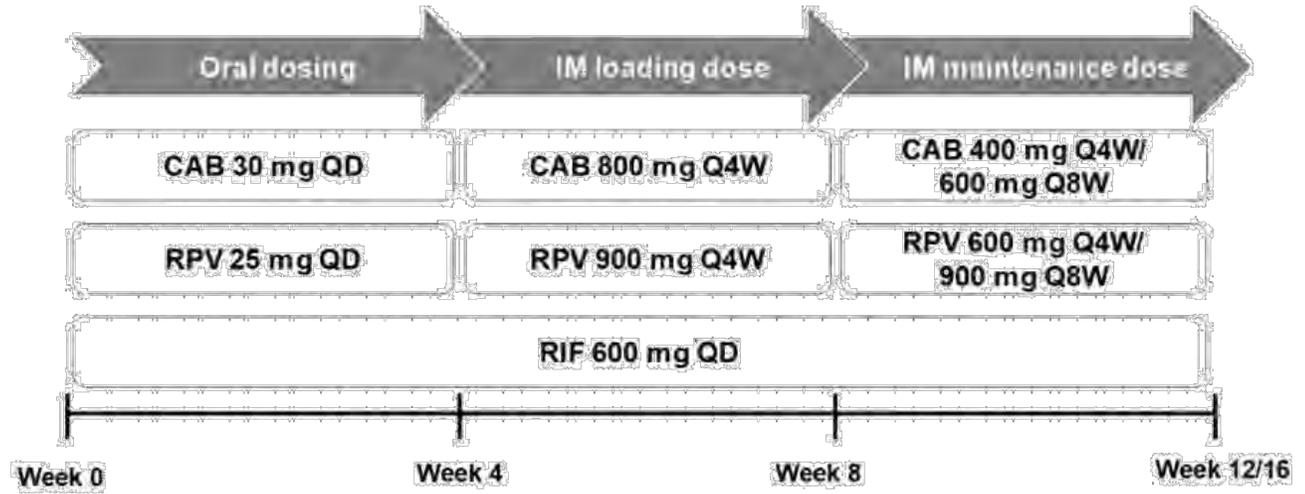
Long-acting cabotegravir

AUC = -25%
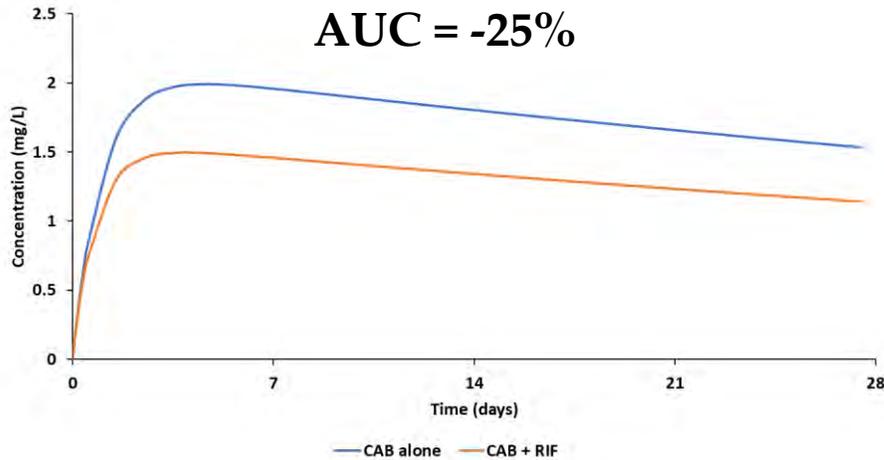
Pharmacokinetic IM cabotegravir (800 mg IM – single) with and without rifampicin (600 mg OD oral)
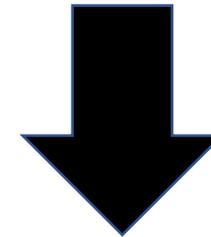
Table 4 Pharmacokinetic summary of drug alone and drug-drug interaction between cabotegravir, rilpivirine long-acting intramuscular formulation vs. 600 mg oral rifampicin

Drug	Drug Alone		Drug + 600 mg OD Rifampin		% difference (alone vs. DDI)		Half-life	
	AUC	C_{trough}	AUC	C_{trough}	AUC	C_{trough}	Alone	Drug + Rif
Cabotegravir 400 mg MD (4-weekly)	1340 ± 295	1.40 ± 0.31	794 ± 186	0.8 ± 0.2	-40.7%	-40.7%	68	65
Cabotegravir 600 mg MD (8-weekly)	2291 ± 541	1.42 ± 0.33	1,247 ± 319	0.77 ± 0.2	-45.6%	-45.8%	69	64
Rilpivirine 600 mg MD (4-weekly)	39,313 ± 22,724	37.3 ± 22.3	7,128 ± 3,128	6.7 ± 2.9	-81.9%	-82.1%	62	59
Rilpivirine 900 mg MD (8-weekly)	59,219 ± 28,134	37.4 ± 17.9	10,175 ± 4,464	6.6 ± 2.9	-82.8%	-82.4%	62	59

MD – maintenance dose. Cabotegravir C_{max}, C_{trough} are expressed as mg/L and AUC in mg.h/L; Rilpivirine C_{max}, C_{trough} are expressed as ng/ml and AUC in ng.h/ml. Half-life is expressed in days. Intramuscular maintenance dose was preceded by 4-weeks of daily oral dose (30 mg- cabotegravir, 25 mg – rilpivirine) and 4-weeks of intramuscular loading dose (800 mg – cabotegravir and 900 mg rilpivirine)

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PBPK Modelling and Rifampicin Induction: Single dose

Figure 4: Single Dose RIF Induction of CYP3A4 & UGT1A1

- - - CYP3A4: RIF 600mg
——— CYP3A4: RIF 1200mg
- - - UGT1A1: RIF 600mg
——— UGT1A1: RIF 1200mg

Note: Greater CYP3A4 induction with 1200 v 600 mg RIF

Figure 5: Ratio of DTG C_{min} Versus the DTG RIF DDI C_{min}

——— DTG 50mg BID with RIF 600mg
——— DTG 50mg BID with RIF 1200mg
——— DTG 100mg BID with RIF 1200mg
——— DTG 50mg TID with RIF 1200mg

Note: In 14 days DTG C_{min} returns to approximately 80% of pre-RIF value – indicating that 14 days is probably sufficient to wait for offset of clinically relevant induction.

Kinvig H et al CROI 2020 Abs 450

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[1]GlaxoSmithKline, Ware, UK; [2]GlaxoSmithKline, Research Triangle Park, NC, USA; [3]ViiV Healthcare, Research Triangle Park, NC, USA; [4]ViiV Healthcare, Nyon, Switzerland

Table 1. Key Input Parameters for CAB PBPK Model

Parameter	Value	Source
Molecular weight	405.4	Measured value
Log P	1.58	Measured value
pKa	7.71	Measured value
Blood/Plasma ratio	0.54	Measured value
Fraction unbound in plasma (Fu)	0.006	Measured value from clinical and *in vitro* investigations
Papp (10^{-6} cm/s)	25.6	Measured value (MDCK)
Vss (L/kg)	0.12	Predicted by Simcyp® (Method 2)
Clearance – enzymatic CL_{int} (µL/min/mg)	UGT1A1 – 4.5 UGT1A9 – 2.2	Measured value from *in vitro* investigations
Transporter inhibition Ki (µM)	OAT1 – 0.4 OAT3 – 0.2	Measured value from *in vitro* investigations ($Ki = IC_{50}/2$)

Figure 3. DDI Predictions of OAT1/OAT3 Substrates When Co-dosed With Repeat Oral CAB 30 mg Dosing
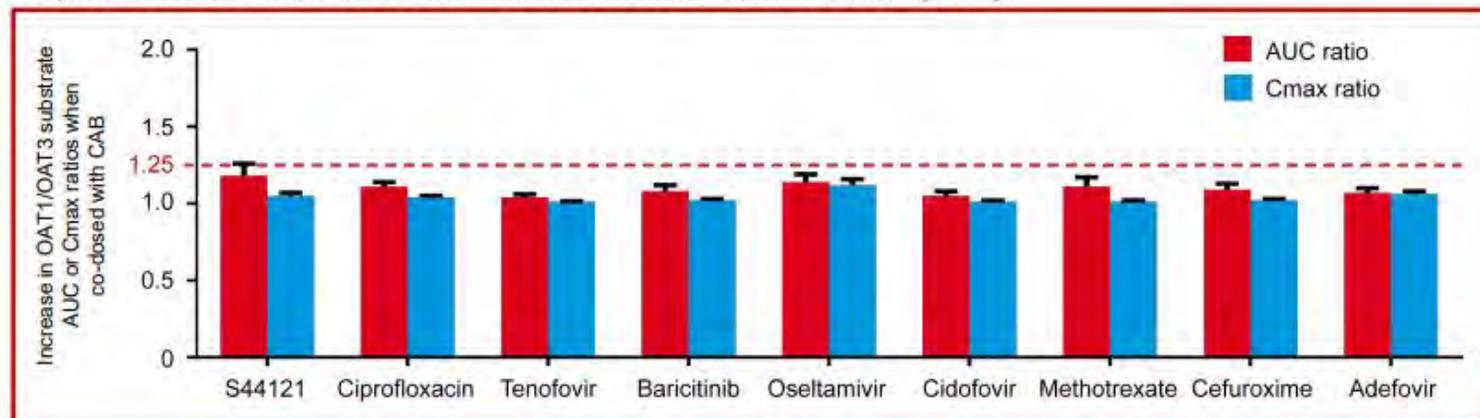

- DDI simulations predicted a mean change in systemic exposure for tested OAT1/OAT3 substrates of <25% after co-administration with CAB at steady state.

Figure 2. Simulated and Observed CAB Plasma Profiles Following Single and Repeat Oral CAB 30 mg Dosing

Solid line = simulated mean CAB plasma profile; dotted lines = simulated 5th-95th percentile; dots = observed individual CAB plasma profiles.

Conclusions

- A PBPK model of CAB was developed and validated that accurately predicted human pharmacokinetics observed in healthy volunteers.

- CAB is predicted to be a clinically weak inhibitor of OAT1/3-mediated transport with mean increase of <25% in systemic exposure of OAT1/3 substrate drugs, such as tenofovir, cidofovir, NSAIDs and methotrexate.

- Sensitivity analyses predicted a mean increase of <25% in systemic exposure of narrow therapeutic index OAT1/OAT3 substrate drugs such as methotrexate even up to 4-fold more potent inhibition values than the measured CAB OAT1/OAT3 IC_{50} or at 3-fold higher CAB oral dose or at 10-fold higher CAB fraction unbound in plasma.

- Similar CAB concentrations following oral and LA administration suggest that these results would apply to CAB LA.

- The predicted lack of interactions supports CAB co-administration with OAT1/OAT3 substrates without dose adjustments.

Blood flows
Organ volume

Plasma protein binding
CYPs expression
GI physiology
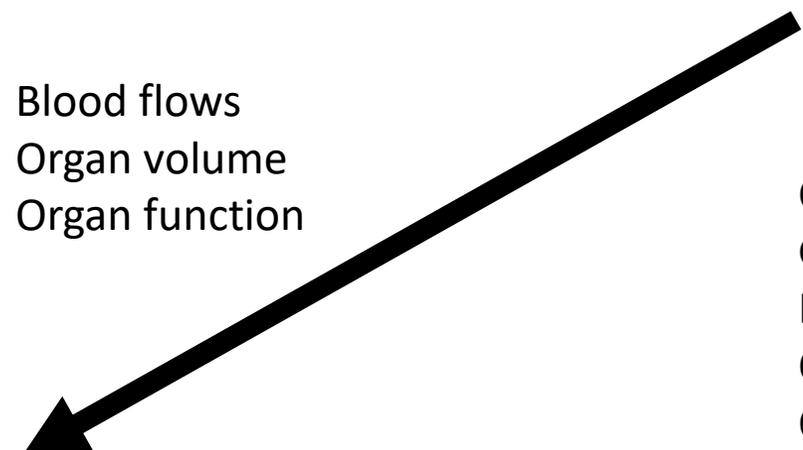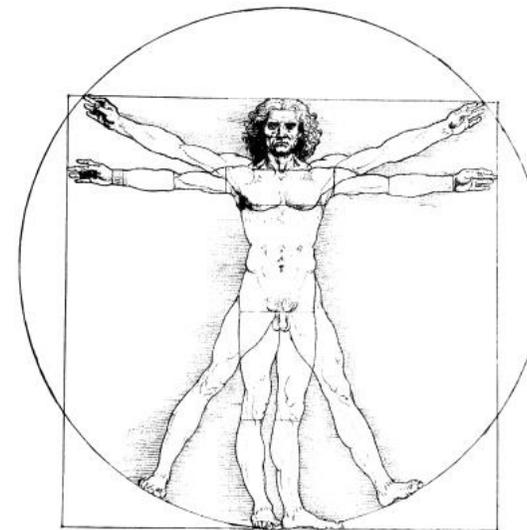
Blood flows
Organ volume
Organ function

CYPs expression
GI physiology
Blood flows
Organ volume
Organ function

Definition of anatomical and physiological characteristics – paediatric population
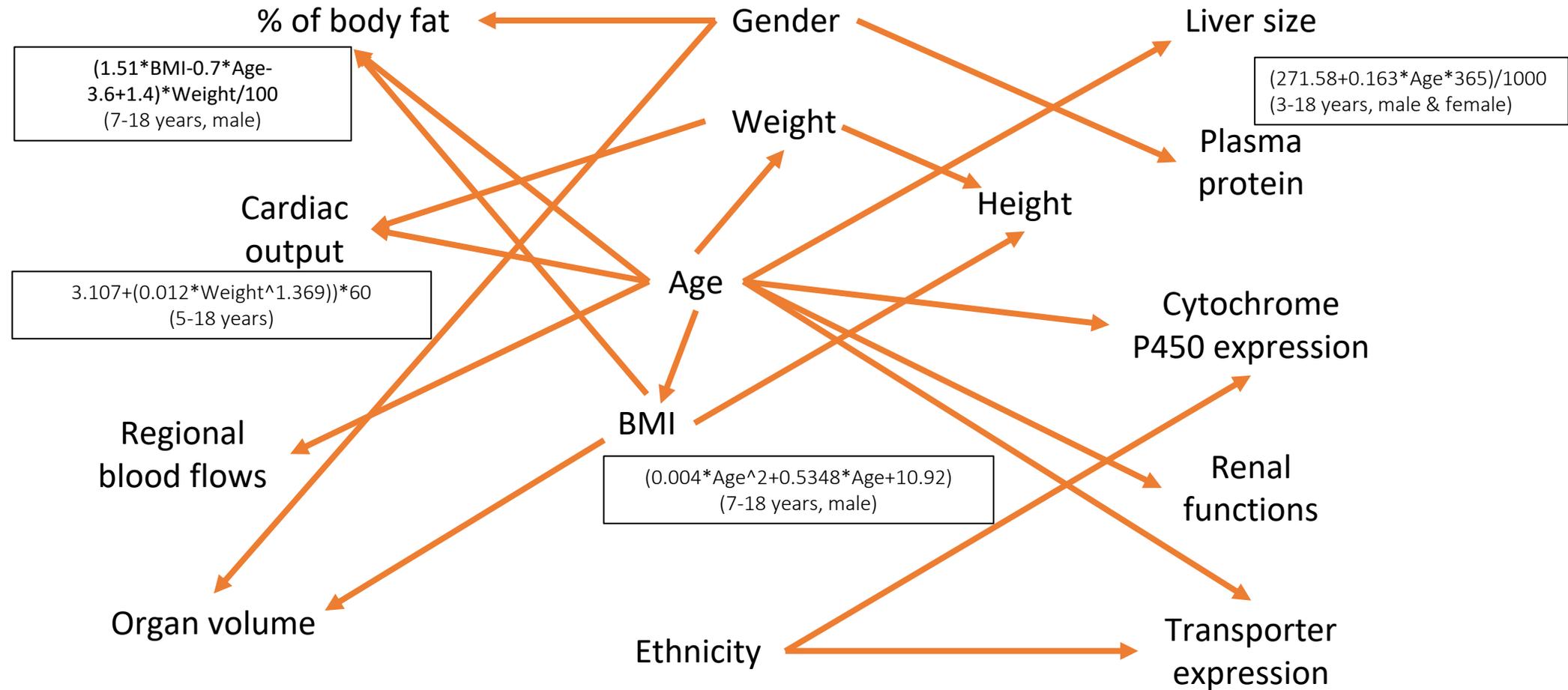
Model validation against adult clinical data

Simulation of theoretical PK children and adolescents

a) cabotegravir
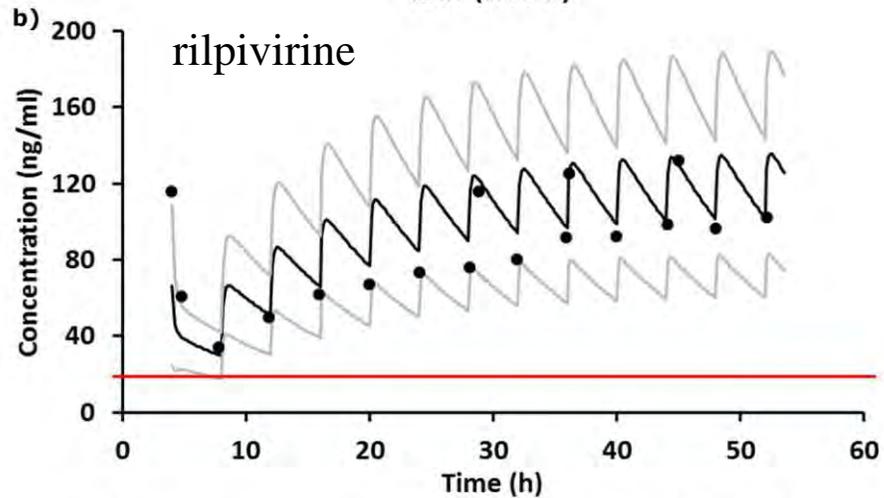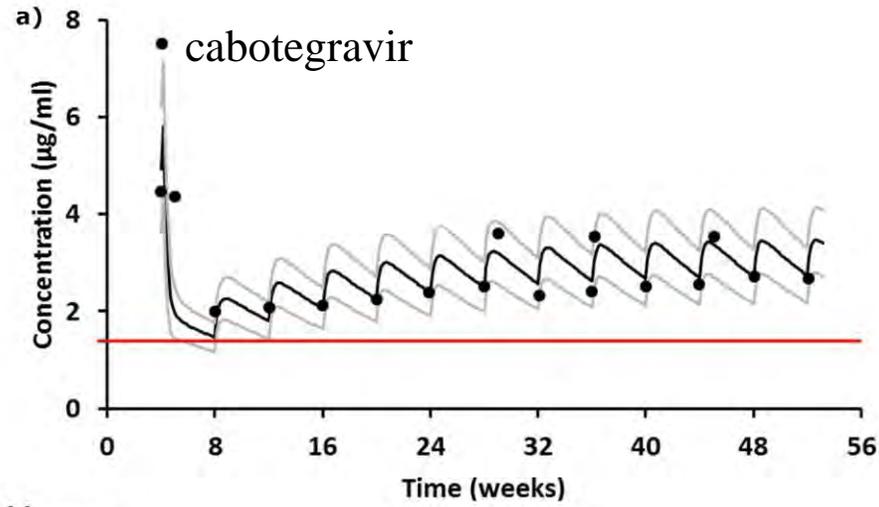
b) rilpivirine

— Simulated mean — Simulated mean ± SD • Clinical Mean
— Target trough concentration

a) 14 - 19.9 kg

b) 25 - 29.9 kg

c) 35 - 39.9 kg

d) 45 - 49.9 kg

e) 55 - 59.9 kg

f) 65 - 69.9 kg
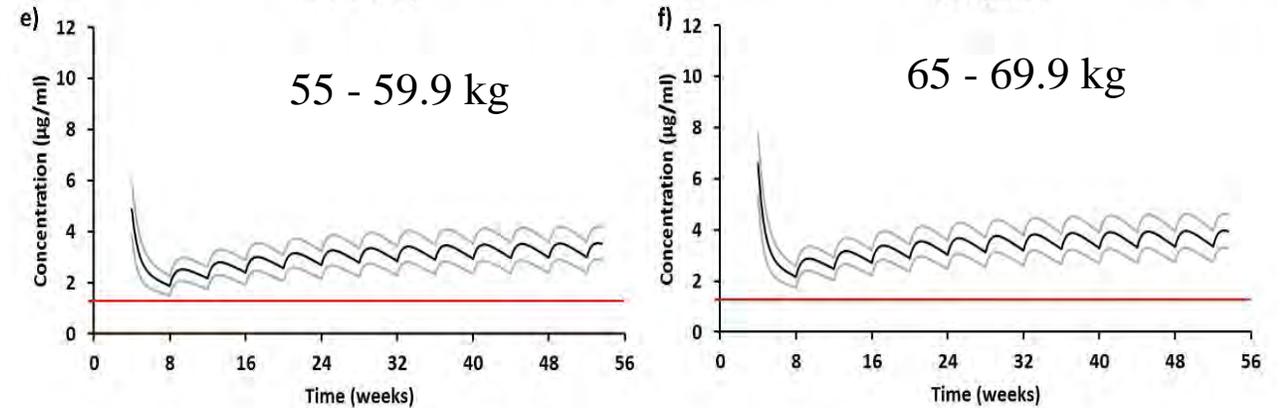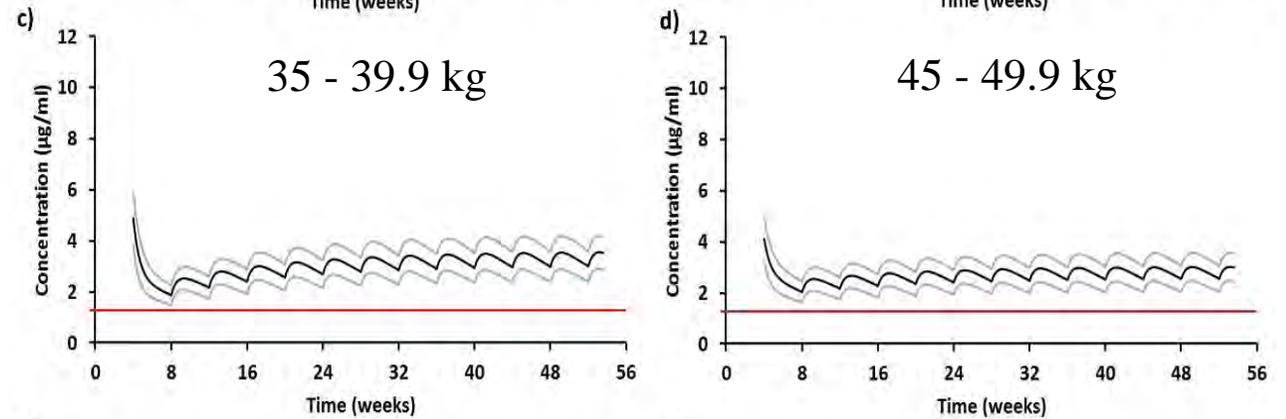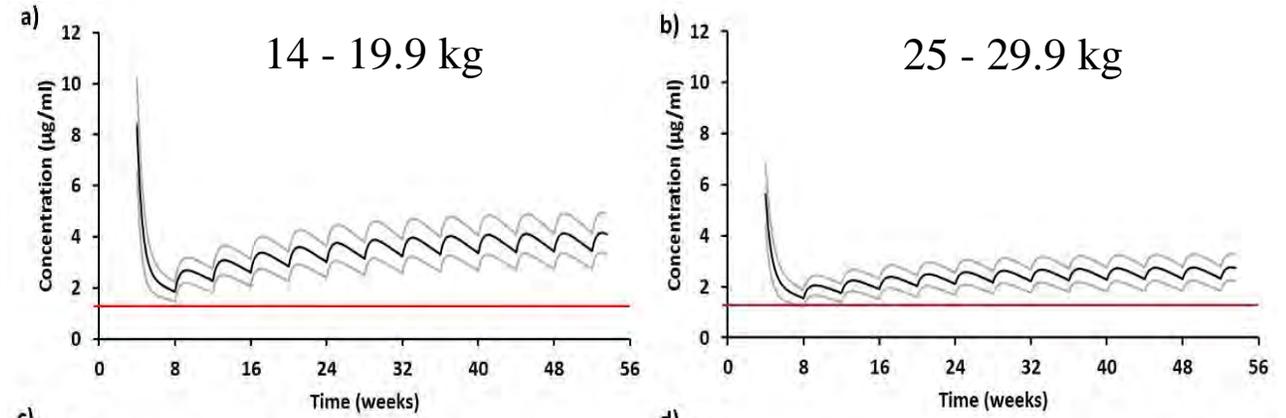
— Simulated mean — Simulated Mean ± SD — Target trough concentration

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Weight (kg)	Rilpivirine			Cabotegravir		
	Oral	Loading dose	Maintenance dose	Oral	Loading dose	Maintenance dose
14 - 19.9	25	250	150	10	200	100
20 - 24.9		250	200		250	100
25 - 29.9		250	200		250	100
30 - 34.9		300	250		350	150
35 - 39.9		350	300		350	150
40 - 44.9		400	300		400	150
45 - 49.9		450	350		450	150
50 - 54.9		450	400	20	450	200
55 - 59.9		500	400		500	200
60 - 64.9		500	450		550	200
65 - 69.9		550	500		600	250
Target concentration (ng/ml)	70 (25 mg PO C_{trough})			1370 (10 mg PO C_{trough})		

Prediction of the dose (in mg) for cabotegravir and rilpivirine for different weight categories of children and adolescents with initial 4 weeks of oral dose followed by IM loading dose and 11 maintenance doses lasting 4-weeks each

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Effect of liver impairment on pharmacokinetics
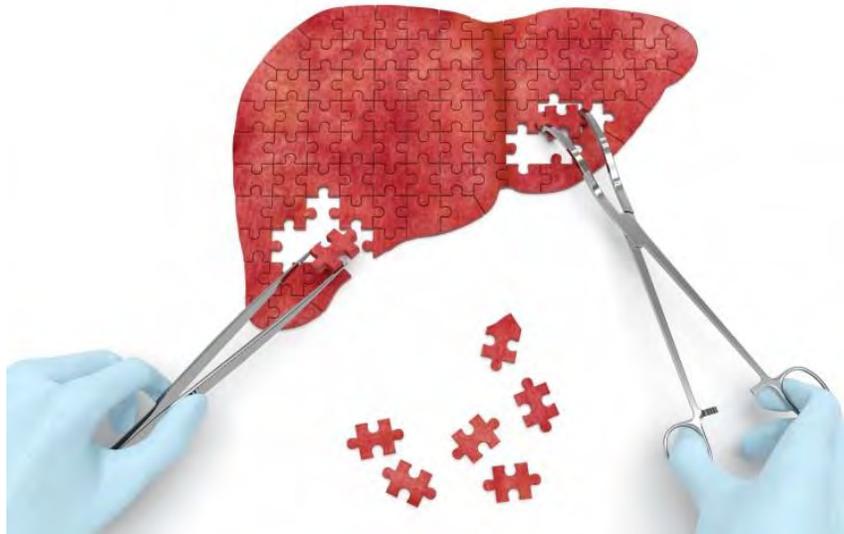
|	Child-Pugh classification								
	A	B	C	A	B	C	A	B	C
	Edginton et al, 2008			Johnson et al, 2010			Li et al, 2015		
Blood flow[1]									
Portal vein	0.4	0.36	0.04	0.91	0.63	0.55	0.72	0.6	0.13
Hepatic arterial	1.3	2.3	3.4	1.4	1.62	1.91	1.5	1.7	2.1
Renal	0.88	0.65	0.48	NA	NA	NA	NA	NA	NA
Other organs	1.75	2.25	2.75	NA	NA	NA	NA	NA	NA
Haematocrit value[2]	39	37	35	36.6	32.9	31.9	38	34	34
Functional liver mass or liver volume fraction[1]	0.69	0.55	0.28	0.81	0.65	0.53	0.91	0.81	0.64
Gut enzyme quantity (CYP3A4)[1]	NA	NA	NA	0.84	0.57	0.35	NA	NA	NA
Hepatic enzyme activity[1]									
CYP3A4	1	0.4	0.4	0.59	0.39	0.25	NA	NA	NA
CYP1A2	1	0.1	0.1	0.63	0.26	0.12	NA	NA	NA
CYP2E1	1	0.83	0.83	0.74	0.48	0.11	NA	NA	NA
GFR[1]	1	0.7	0.36	0.7	0.58	0.55	NA	NA	NA
Cardiac output[1]	1.11	1.27	1.36	1.16	1.32	1.4	1.1	1.2	1.3
Albumin[3]	36.2	30.4	22.4	41.1	33.9	26.3	37.5	30.8	23.7
Glycoprotein[3]	0.48	0.45	0.24	0.57	0.52	0.46	NA	NA	NA

GFR, glomerular filtration rate, *NA*, not applicable; 1 = Fractions of control values, 2 = Percentage (%) and 3 = Concentration (g/L)

Model validation

RPV simulations – 25mg OD

Variables	Observed	Simulated	AAFE
AUC (ng.hr/mL) - Control	2708	2681	1,010
AUC (ng.hr/mL) - CP-A	2844	2380	1,195
AUC (ng.hr/mL) - CP-B	3981	4987	1,252
AUC (ng.hr/mL) - CP-C		5370	
Cmax (ng/mL) - Control	111	103	1,076
Cmax (ng/mL) - CP-A	106	94	1,121
Cmax (ng/mL) - CP-B	141	171	1,212
Cmax (ng/mL) - CP-C		176	
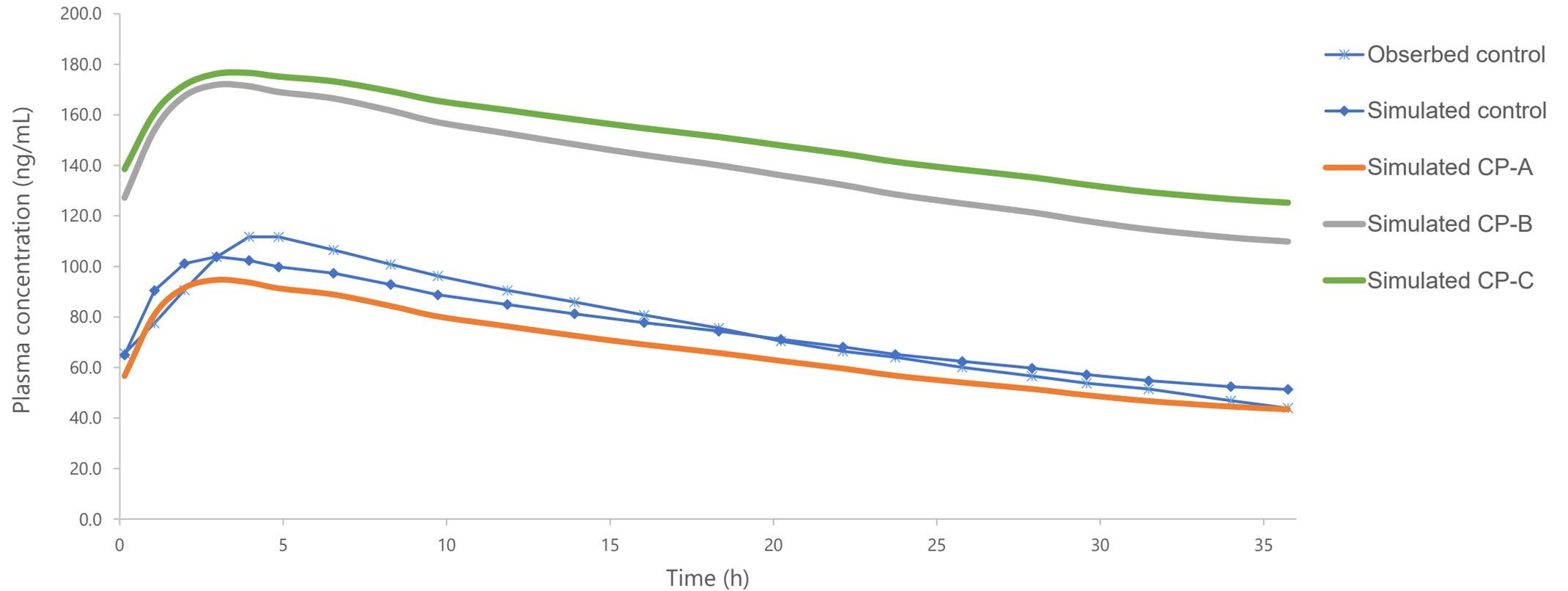
Model prediction

LA RPV simulations 1200/900mg IM

| Variables	Observed	Simulated	AAFE / %		Fold	Mean %
AUC (ng.hr/mL) - Control	209494	253706	1,21			
AUC (ng.hr/mL) - CP-A		243539	-4,01%		0,95	CP-A
AUC (ng.hr/mL) - CP-B		499702	96,96%		1,96	-4,34%
AUC (ng.hr/mL) - CP-C		570883	125,02%		2,25	
Cmax (ng/mL) - Control	154,4	172,2	1,12			
Cmax (ng/mL) - CP-A		167,3	-2,87%		0,97	CP-B
Cmax (ng/mL) - CP-B		314,2	82,43%		1,82	94,72%
Cmax (ng/mL) - CP-C		365,3	112,09%		2,12	
Ctrough (ng/mL) - Control	74,4	86,0	1,16			
Ctrough (ng/mL) - CP-A		80,7	-6,14%		0,93	CP-C
Ctrough (ng/mL) - CP-B		176,2	104,78%		2,04	123,10%
Ctrough (ng/mL) - CP-C		199,8	132,21%		2,32	
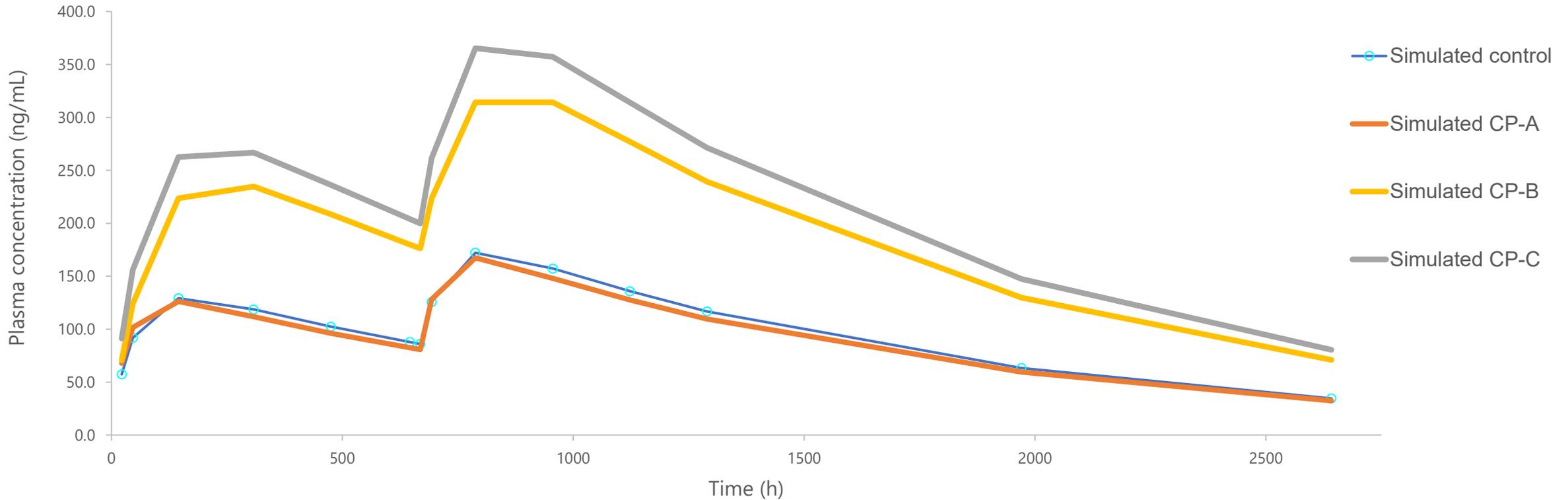
Other clinical scenarios
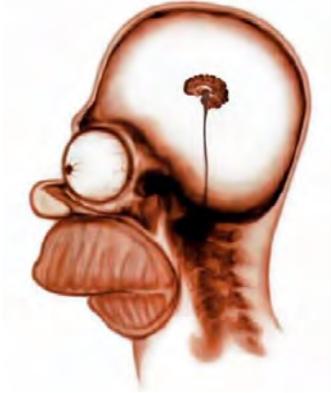
Penetration into tissues
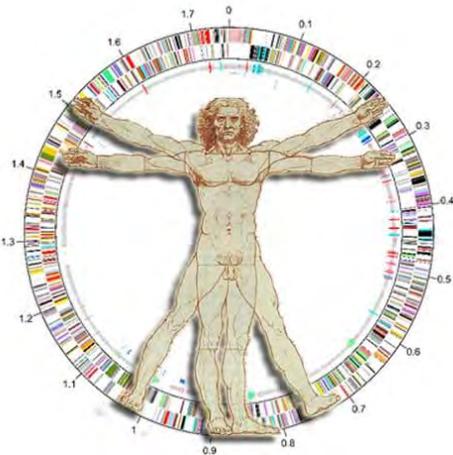
Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.

[CAB] subsequent to final injection (log scale) - Males
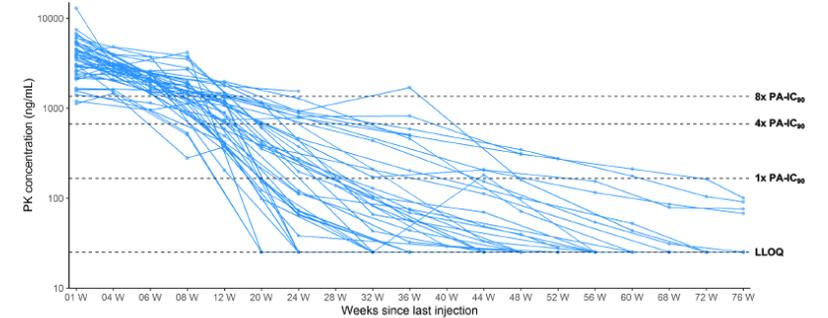
Management of the PK tail, bridging and dosing schedule

Pharmacogenetics

Dose reduction and simplification

Simulation of long acting dosing - TB

IM Dose – 2000 mg/30 days   IM release rate – 0.0025 h^{-1}

Drug	AUC (Mean ± SD) (µg.h/ml)	C$_{max}$ (Mean ± SD) (µg/ml)	C$_{trough}$ (Mean ± SD) (µg/ml)	Cut-off limit (µg/ml)
Bedaquiline	271 ± 65	0.72 ± 0.16	0.14 ± 0.04	1.6 (ECOFF)
Delamanid	89 ± 16	0.23 ± 0.04	0.05 ± 0.01	0.04 (ECOFF)
Rifapentine	1639 ± 160	4.12 ± 0.38	0.88 ± 0.09	0.06 (MIC)
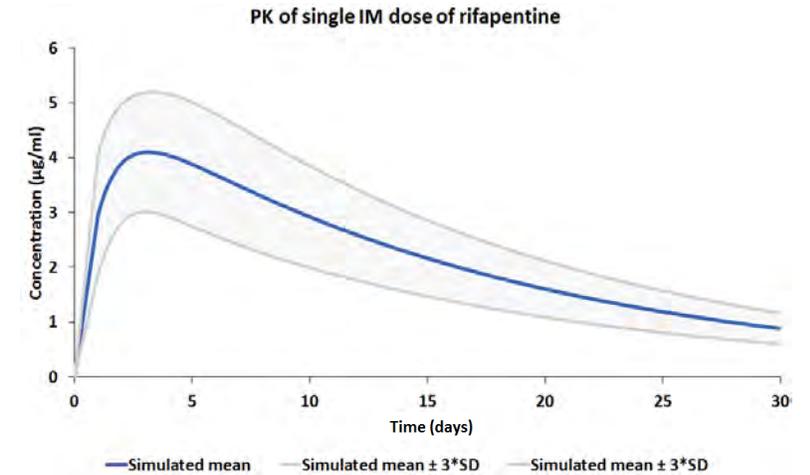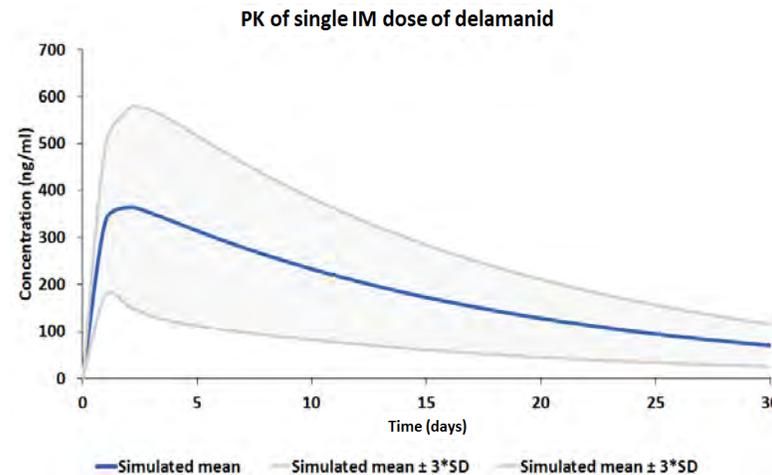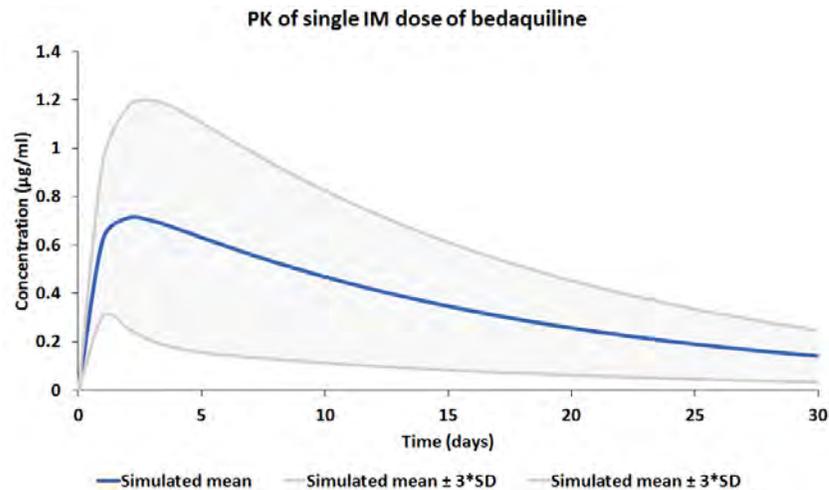
Optimisation of dosing and formulation characteristics
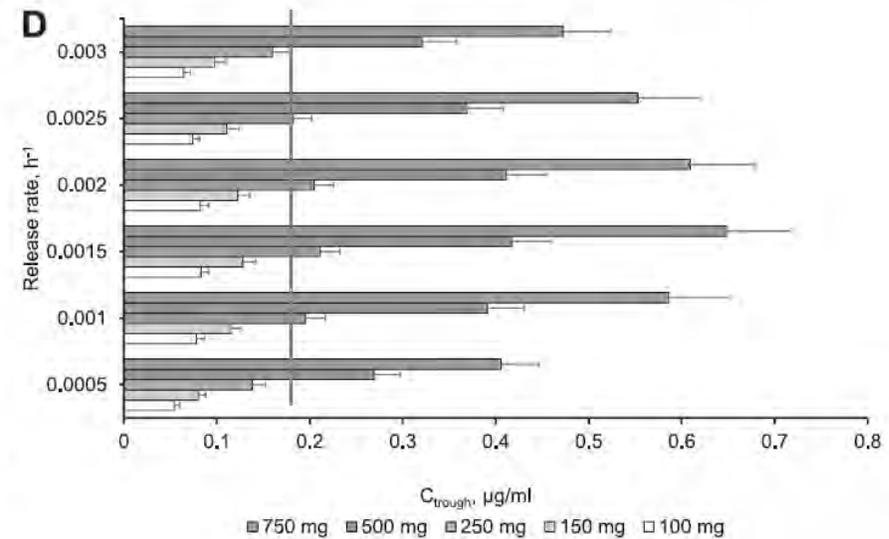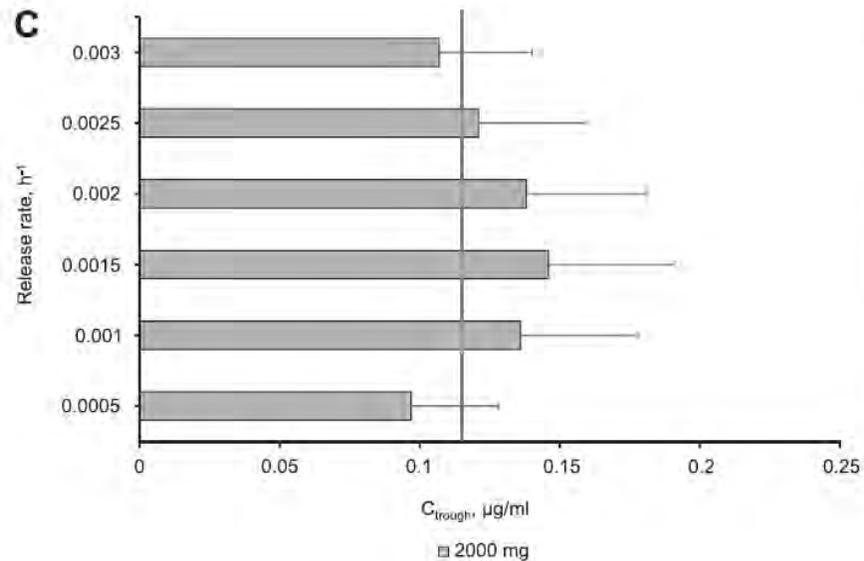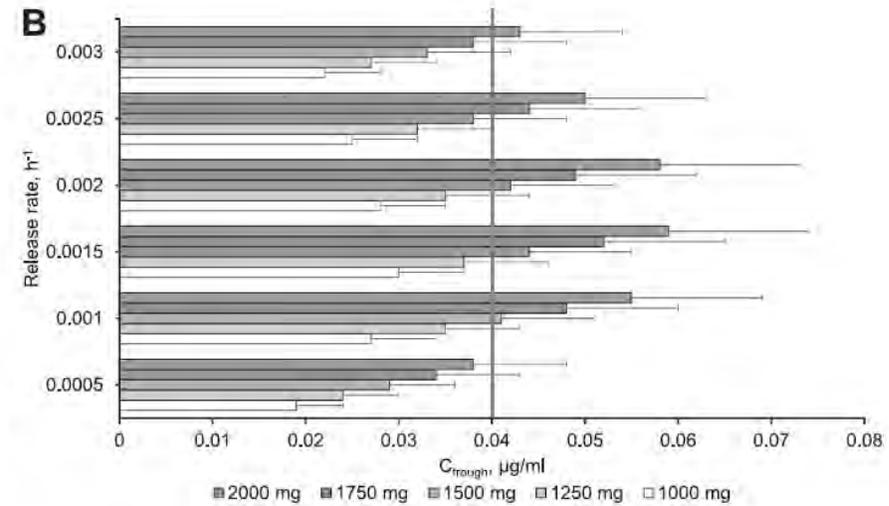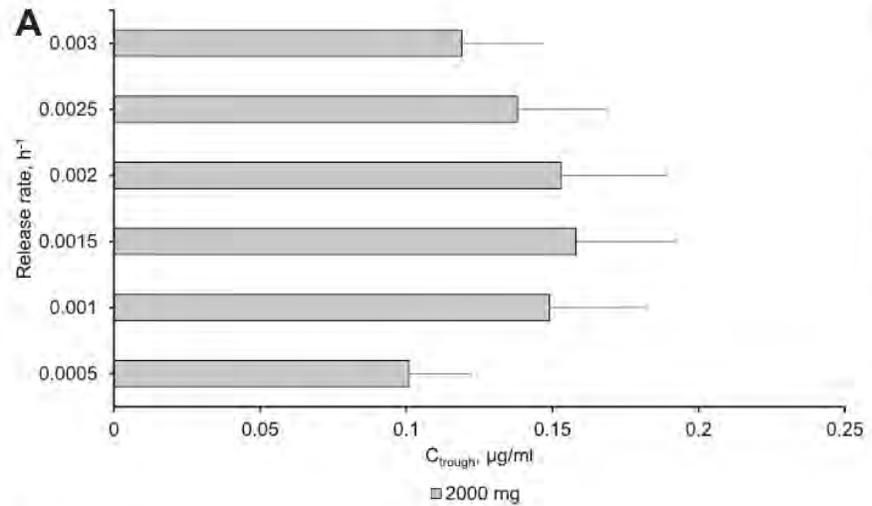
A) bedaquiline **B)** delamanid **C)** isoniazid **D)** rifapentine

Predicting Pharmacokinetics of a Tenofovir Alafenamide Subcutaneous Implant Using Physiologically Based Pharmacokinetic Modelling

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[a]Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom
[b]RTI International, Durham, North Carolina, USA
[c]Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Baltimore, Maryland, USA
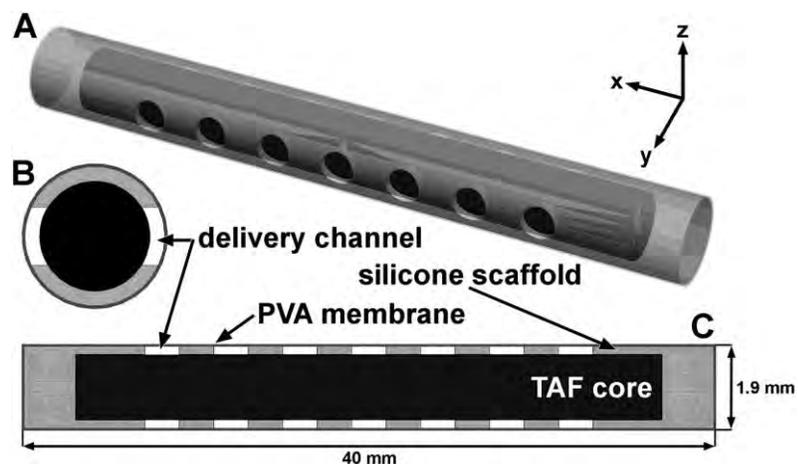
TABLE 2 TFV-DP cervical and rectal PKs for a subcutaneous implant at different zero-order release rates for 28 consecutive days

Release rate (mg/day)	Simulated TFV-DP concn (fmol/10^6 cells; mean $\pm$ SD) in[a]:		
	PBMCs	Cervical tissue	Rectal tissue
1.6	56.6 $\pm$ 15.8	1.72 $\pm$ 0.38	1.11 $\pm$ 0.25
1.5	51.7 $\pm$ 13.5	1.63 $\pm$ 0.42	1.05 $\pm$ 0.27
1.4	49.3 $\pm$ 10.3	1.52 $\pm$ 0.32	0.98 $\pm$ 0.21
1.3	46.3 $\pm$ 11.1	1.45 $\pm$ 0.36	0.94 $\pm$ 0.23

[a]Average ratios of 0.031 and 0.02 for TFV-DP cervical/TFV-DP PBMC and TFV-DP rectal/TFV-DP PBMC were used for computation of TFV-DP concentrations in cervical and rectal tissues, respectively.
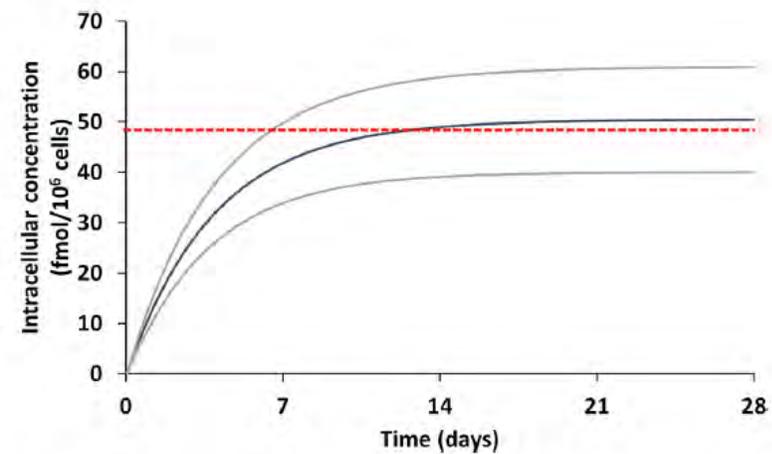

FIG 2 TFV-DP pharmacokinetics at a constant release of 1.4 mg/day TAF implant through the subcutaneous tissue for 28 consecutive days. Red line, target intracellular concentration of 48 fmol/10^6 cells; blue line, simulated TFV-DP mean; gray line, simulated TFV-DP mean $\pm$ 1 SD.

Microneedle array patches

Skin patch*

OPTION 1
HYDROGEL MICROARRAY PATCH

User applies patch to skin, wears continuously for about one week, and then reapplies.

Rilpivirine diffuses slowly from patch reservoir (Fig. 1) through hydrogel microarray into body, maintaining sustained and clinically effective systemic concentrations (Fig. 2).

Fig. 1   Fig. 2

Fig. 1   Fig. 2
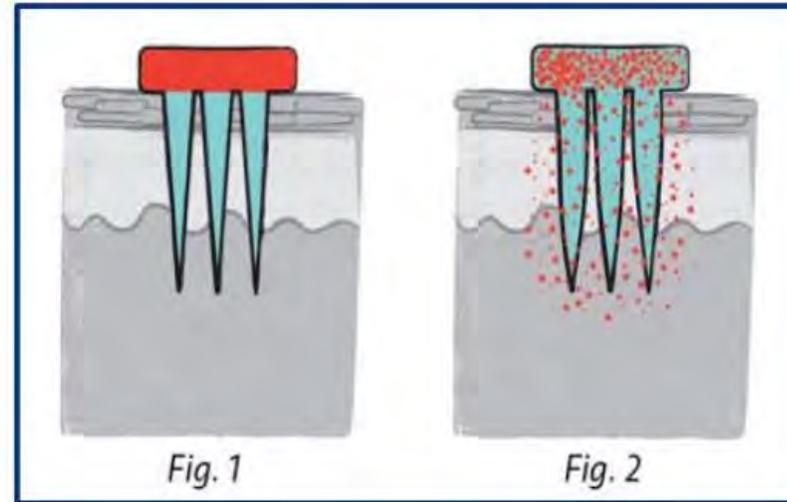
Polymeric MAPs release their drug payload as they swell, dissolve, or biodegrade in the viable skin layers.

• Discreet administration at home:

• Simplified logistics and reduced service delivery costs

• Pain free

• Possibility of targeting lymphatic HIV reservoirs

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PBPK Modelling of Microarray Patches for Long-acting Intradermal Drug Delivery

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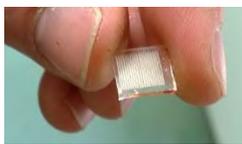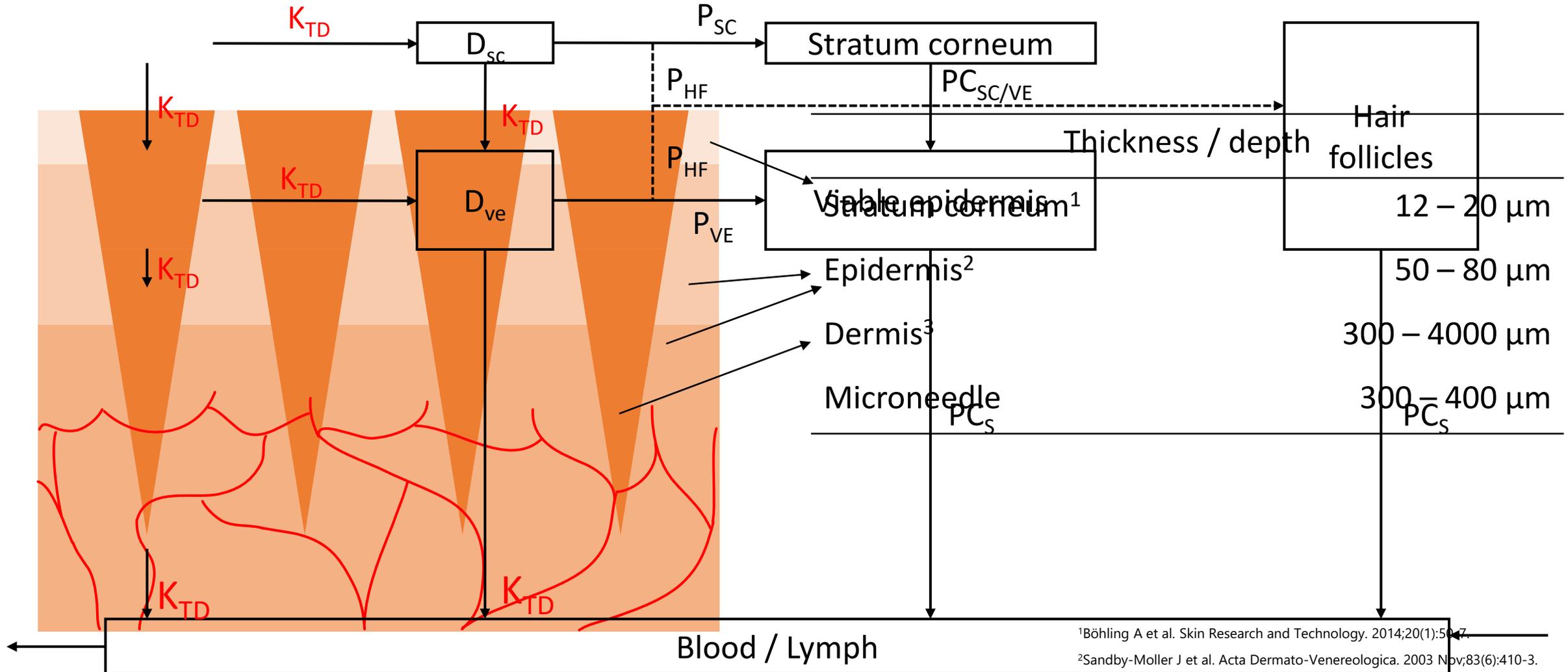
[1]Böhling A et al. Skin Research and Technology. 2014;20(1):50-7.

[2]Sandby-Moller J et al. Acta Dermato-Venereologica. 2003 Nov;83(6):410-3.

[3]Bergman RA et al. Atlas of Microscopic Anatomy - A Functional Approach; 1999.

Cabotegravir intradermal monthly vs intramuscular bimonthly

## Intradermal 540 mg LD, 360 mg MD (1 × 10^{-3} h^{-1})
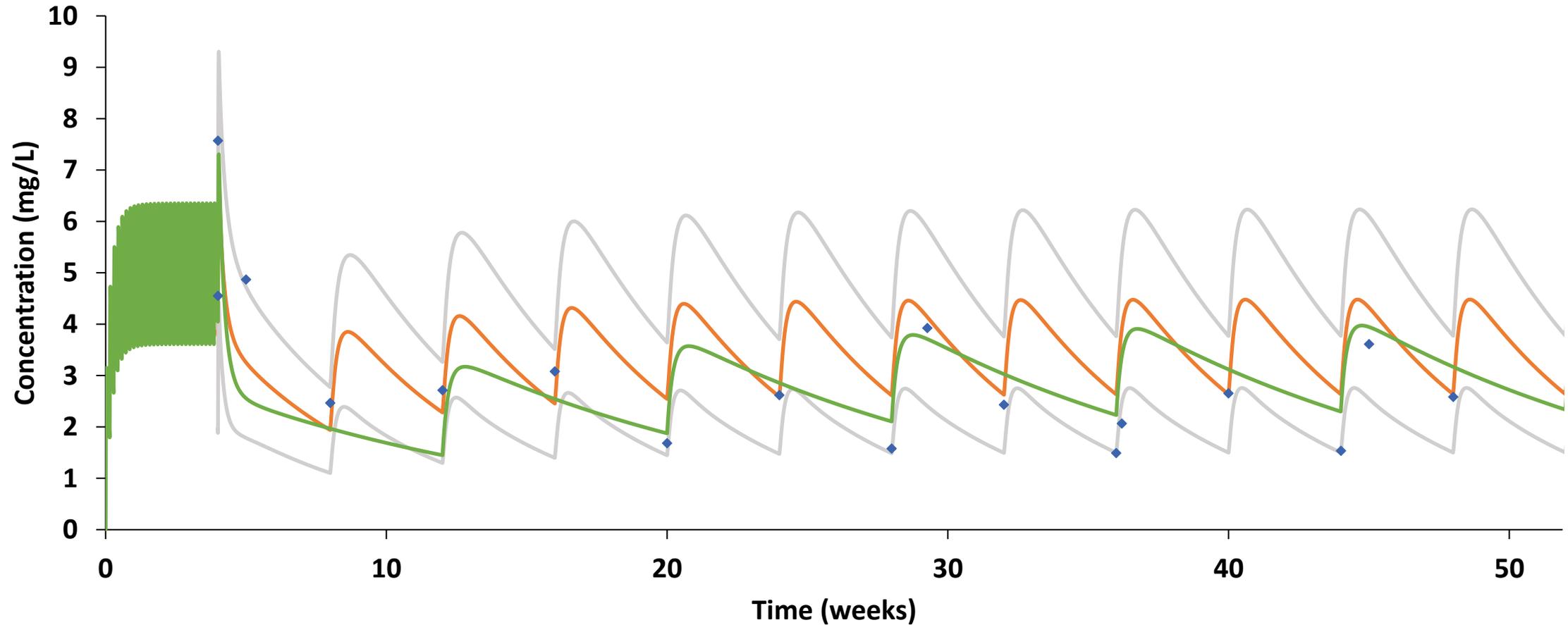
Legend: Intradermal mean — Intradermal mean ± SD — IM simulated mean — LATTE-2 mean PK

TAF MAP: 7 Days with No Loading Dose

Release Rates

- 0.0005
- 0.0025
- 0.005

MAP 7 Days with No Loading Dose: 10mg
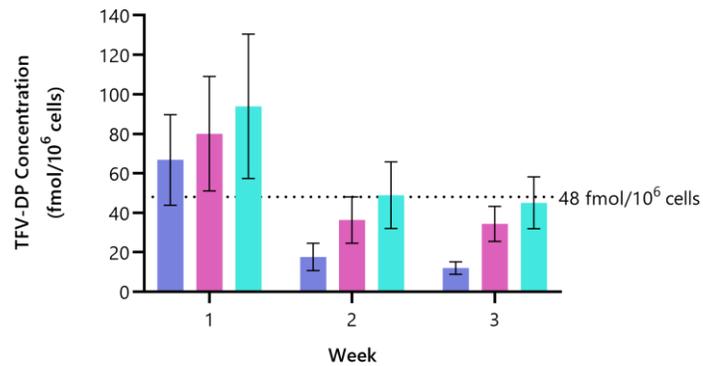
MAP 7 Days with No Loading Dose: 20mg

MAP 7 Days with No Loading Dose: 30mg

10mg MAP with a release rates of 0.0025 h^{-1} and 0.005 h^{-1} achieved a C_{min} greater than 48 fmol/10^6 cells over 3 weeks.
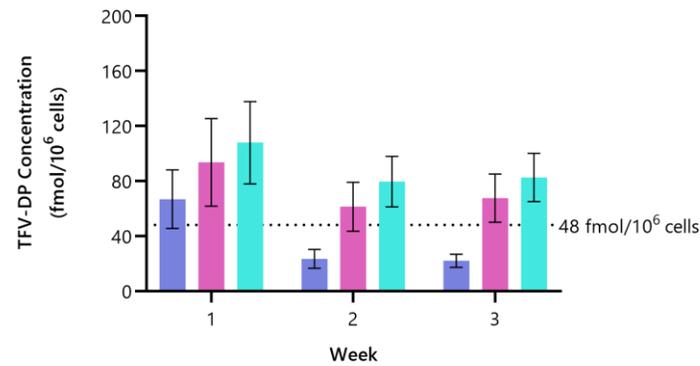
20mg MAP with a release rates of 0.0025 h^{-1} and 0.005 h^{-1} achieved a C_{min} greater than 48 fmol/10^6 cells over 3 weeks.
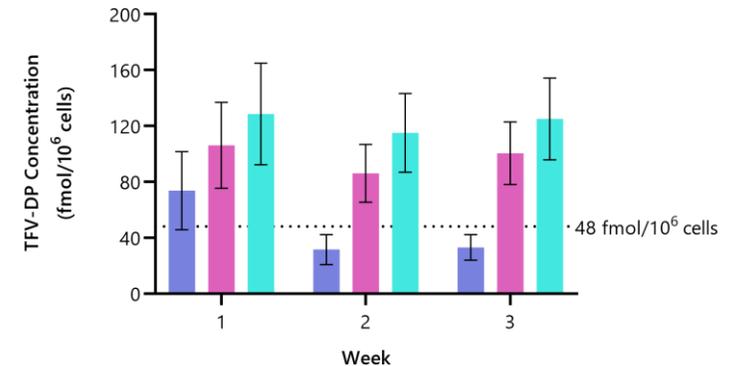
30mg MAP with a release rates of 0.0025 h^{-1} and 0.005 h^{-1} achieved a C_{min} greater than 48 fmol/10^6 cells over 3 weeks.

Is this approach relevant?

Extracts from FDA/EMA guidelines:

PBPK has **great potential value to support benefit–risk evaluations**

PBPK provides **a mechanistic basis for extrapolation beyond the clinical trial population**, reducing uncertainty, and **enabling better labeling** around drug–drug interactions and in special populations

"PBPK-thinking" in drug development is encouraged, as it leads to a mechanistic understanding of the processes mediating drug disposition

Regulatory guidelines

Physiologically Based Pharmacokinetic Analyses — Format and Content
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Office of Clinical Pharmacology at 301-796-5008 or OK.Pui.Ida.Shia.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical Pharmacology

5. Software

The FDA does not require the use of a particular PBPK modeling software. Because of substantive differences in software models and versions, sponsors should include information on the PBPK modeling software. Table 1 below highlights the information that should be included regarding commercial PBPK modeling software (commercial PBPK platform) versus custom modeling software (e.g., commercial software that has been modified with custom codes or otherwise revised for the purpose of PBPK modeling).

Table 1. Software Information for PBPK Modeling

| Suggested Software Information	PBPK Models	
	Custom Modeling Software	Commercial PBPK Platform
Name and version of the software	Yes	Yes
Schematic view of model structure and differential equations based on established theoretical or biological basis	Yes	Optional
Parameterization of system information and sources of parameter values	Yes	Optional
Table of drug-dependent parameters for the investigational drug of interest, including names, values, units, and sources of the parameters, prediction algorithms, and assumptions being made	Yes	Yes
Literature references and the sponsor's prior experience/knowledge in using the software for PBPK modeling (to help the reviewer understand how PBPK models are coded using the modeling software that was tested)	Yes	Yes
Manuals on model implementation of the software (to be provided as supporting documents)	Yes	Optional
Library system models (e.g., virtual population), including justifications for any modifications made to the model's physiological parameters by the sponsor	Not applicable	Yes
Library drug models, including justifications for any modifications to the model made by the sponsor and information on model verification	Not applicable	Yes

Modelling limitations
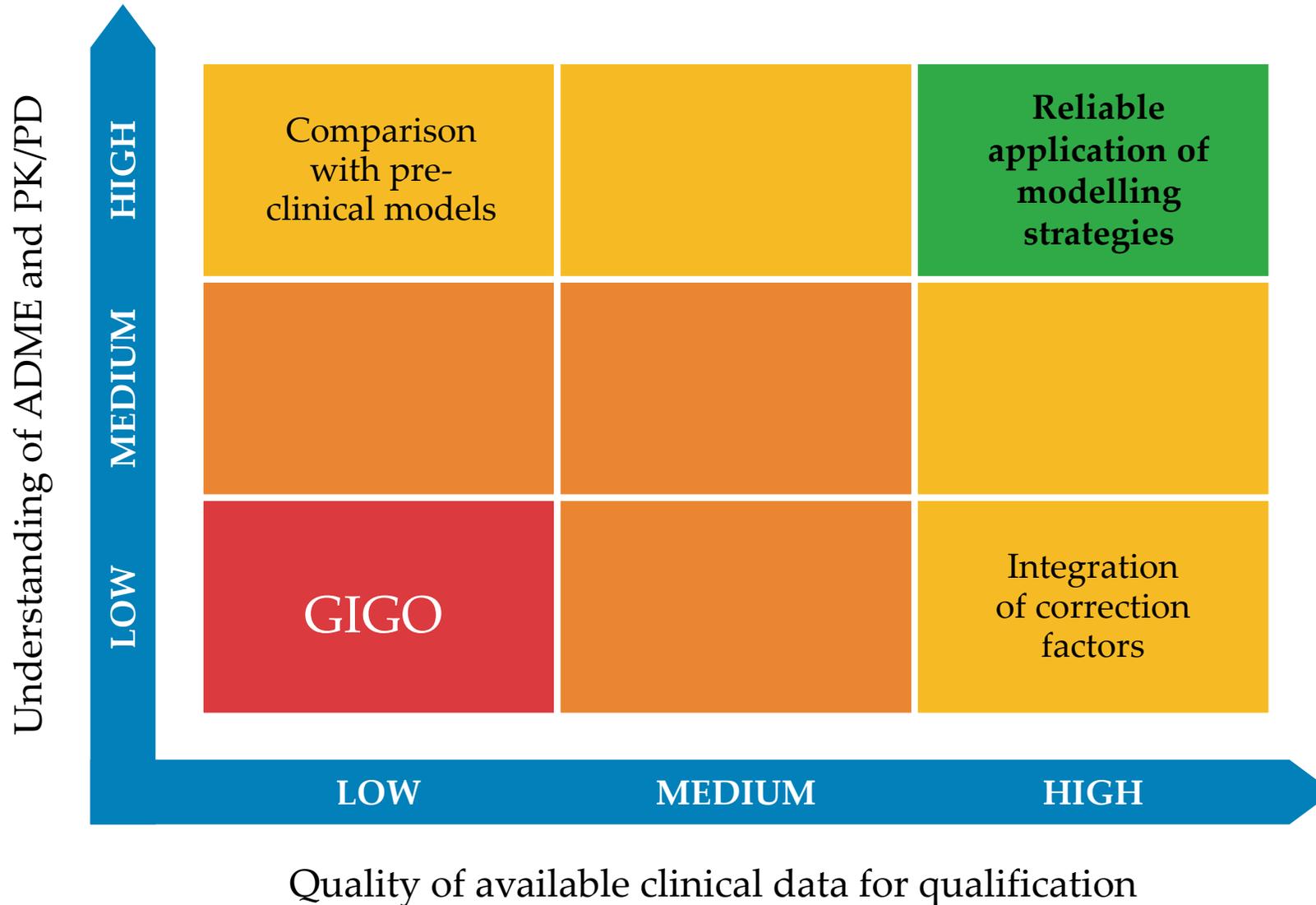
The GIGO Principle

The domino-butterfly effect

SUGGESTED DOSE
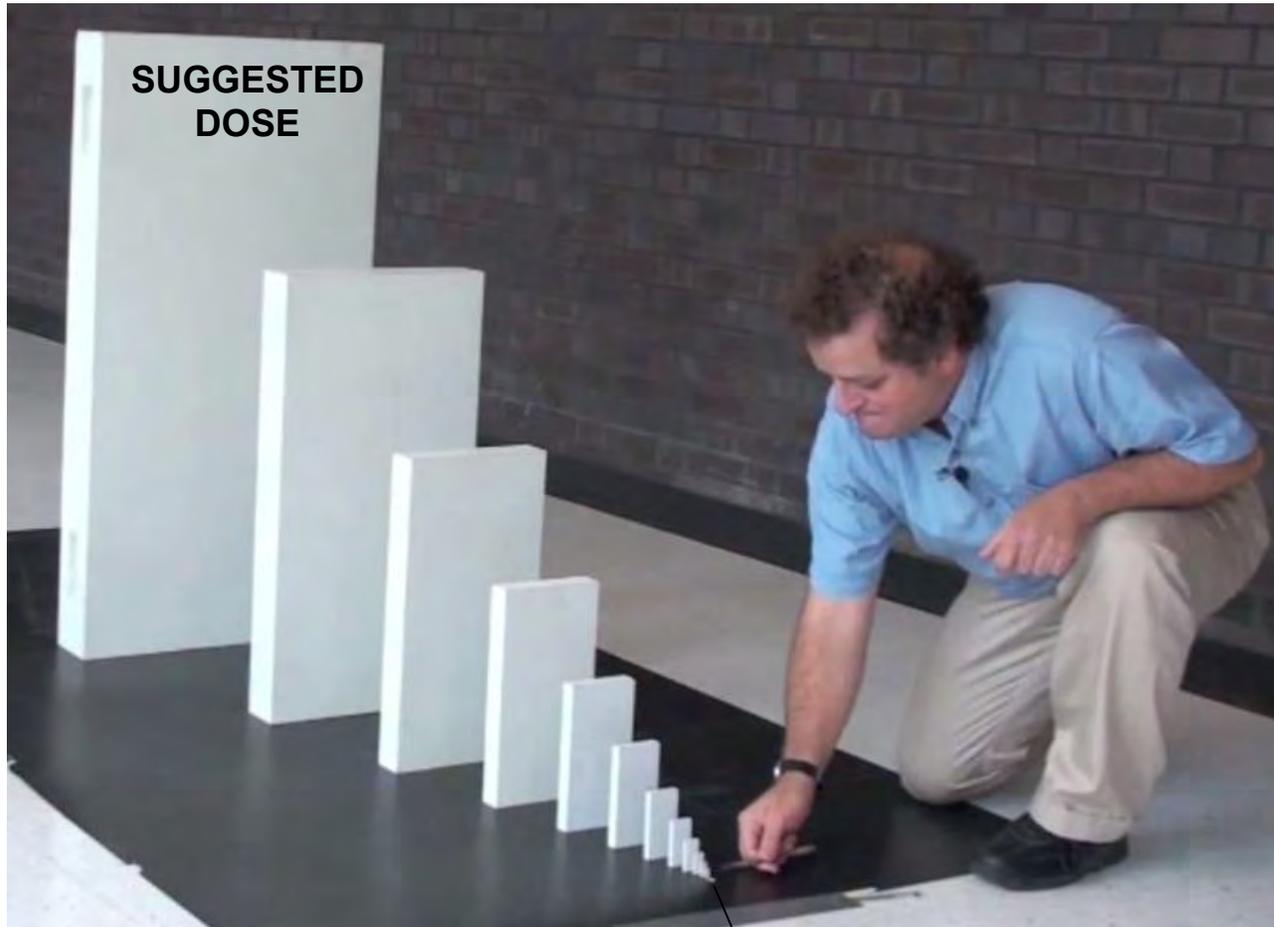
APPARENTLY INSIGNIFICANT CONSTANT

- Complex computational framework

- Variability in experimental approaches

- In vitro in vivo extrapolation

- Unknown mechanisms

- Poorly characterised patient specific factors

- Inappropriate correction for experimental factors

"Remember that hurricane a thousand miles away? That was me!"

Model development and application
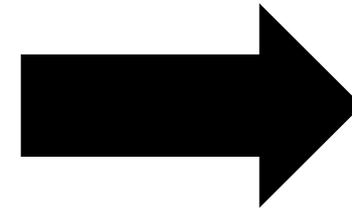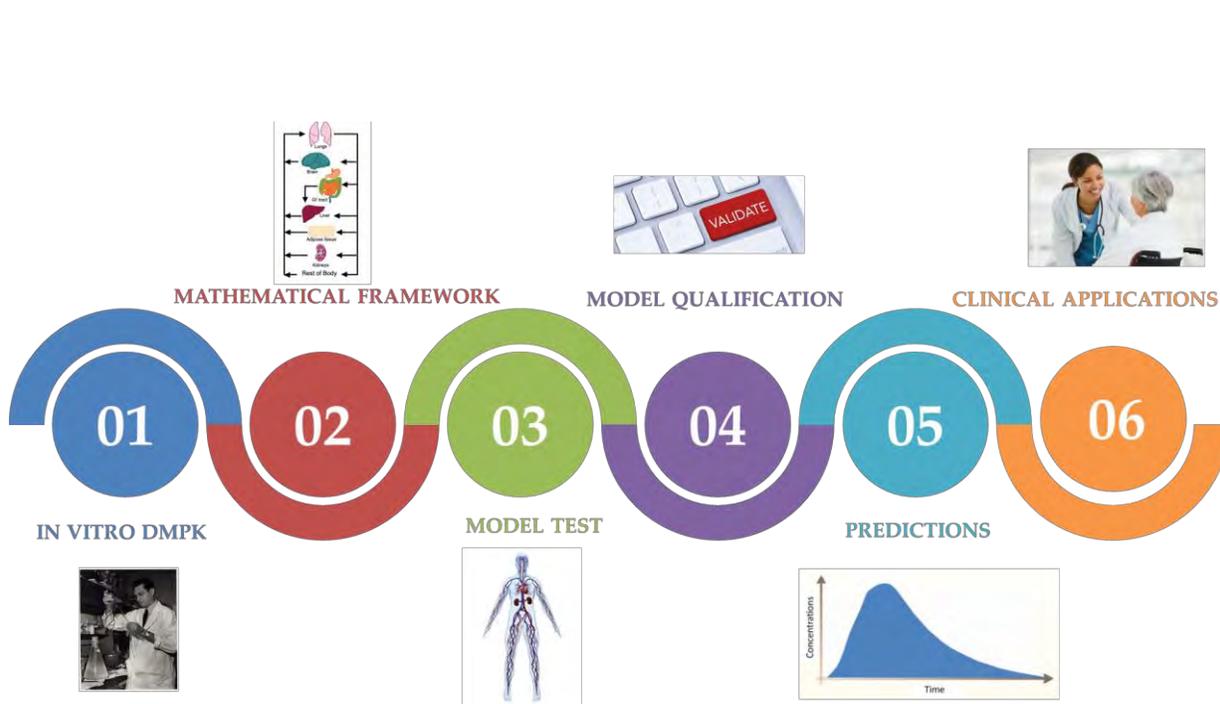
- Complex computational framework
- Variability in experimental approaches
- In vitro in vivo extrapolation
- Unknown mechanisms
- Poorly characterised patient specific factors
- Inappropriate correction for experimental factors

Dynamic interplay

CLINICAL
- Description of patient characteristics
- Identification of clinical challenges
- Design of clinical studies
- Supporting rational prescription

DRUG/FORMULATION DEVELOPMENT
- Identification of "DDI-prone" candidates
- Streamline selection of drugs
- Rational design of formulations
- Transfer across platforms

MECHANISMS
- Description of novel ADME processes
- Optimisation of experimental methods
- In vitro in vivo extrapolation
- Use of pre-clinical models

MODELLING
- Integration with population-based models
- Inform machine learning algorithms
- Quantitative systems pharmacology
- Transfer of models across platforms

PBPK and PK/PD MODELLING

Take home messages

- Mechanisms underpinning LA formulation PK are different than oral formulations

- Absorption rate is the main factor controlling half-life

- DDIs are different than oral drugs but are relevant

- Dose stratification for patient populations might be necessary

- Modelling is an impactful tool (with limitations!) to rationalise the development and clinical management of long acting formulations

Acknowledgements