Simulation of first-in-human using an allometrically scaled population mechanistic TMDD model with preclinical monkey data

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Introduction

- **First-in-human**: what dose to choose to elicit the desired effect (efficacy), without causing harm (safety)?
- Translation of the preclinical information to human clinical trials is **challenging**.
- **Scaling** of the 'No Adverse Effect Level' dose based on body-weight or BSA has proven its limits, especially for biologics.

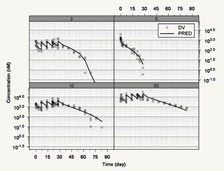
Can we accurately predict the human PK using a model fitted on preclinical data?

Case study with MonolixSuite on PF-03446962, an IgG2 antibody directed against ALK1 receptor (antiangiogenic target) with nonlinear PK.

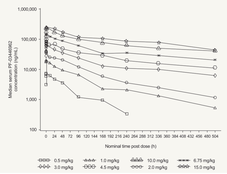
Monkey preclinical PK

- 14 monkeys
- single or multiple doses
- Dense data

Luu KT et al. (2012). *Journal of Pharmacology and Experimental Therapeutics*, *341*(3), 702–708.



Translation possible ?



Human phase I PK

- 8 dose levels
- averaged data (n=6)

Goff LW et al. (2016). *Clinical Cancer Research*, 22(9), 2146–2154.

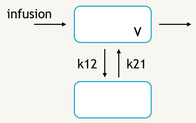
Modeling of the monkey data with Monolix

Three different models of increasing complexity are used to fit the preclinical monkey PK data, using a population approach in Monolix.

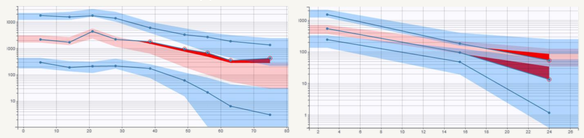
Model scheme | **Estimated parameters** | **VPC for single and multiple doses**

2-compartment model

Does not capture properly the data, in particular the nonlinear elimination apparent in the data.

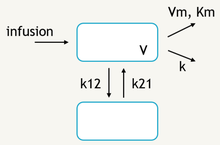


	Value	CV
V/F	22.0 mL/kg	15.8%
k	0.214 /day	27.4%
k12	1.15 /day	49.1%
k21	0.786 /day	23.0%

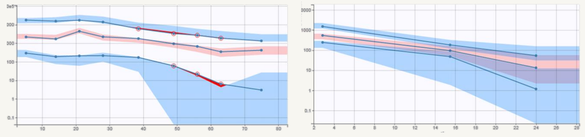


TMDD Michaelis-Menten model

Does capture properly the data.

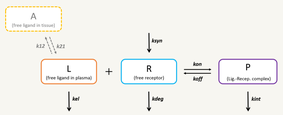


	Value	CV
V/F	22.1 mL/kg	20.1%
k	0.141 /day	9.2%
k12	0.765 /day	10.8%
k21	0.393 /day	12.6%
Vm	34.7 nM/day	31.9%
Km	12.3 nM	79.6%

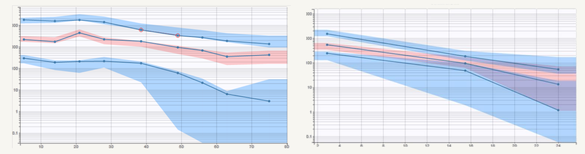


TMDD Quasi-equilibrium model

Does capture properly the data.



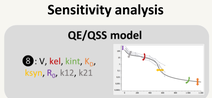
	Value	CV
V/F	22.2 mL/kg	17.3%
k	0.153 /day	14.7%
k12	0.846 /day	20.4%
k21	0.424 /day	15.6%
R0	1.27 nM	30.1%
kint	14 /day (fixed)	-
kdeg	20.1 /day	37.3%
KD	2.4 nM (fixed)	-



The TMDD QE model has 8 parameters. According to the sensitivity analysis, KD and kint will not be identifiable. Luckily, experimental values are available for these 2 parameters.

Sensitivity analysis

QE/QSS model



Experimental values

	Value	Experiment
kint	14 /day	internalization via FACS
KD	2.4 nM	surface plasmon resonance

Prediction of human PK using Simulx

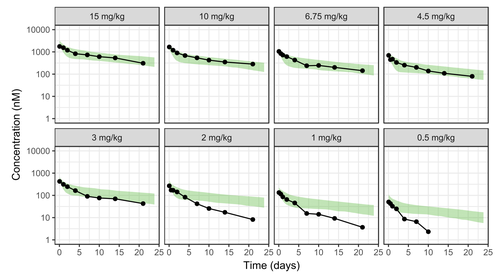
The parameters obtained on monkeys are scaled to human using simple allometric scaling for the linear PK parameters, no change for Vm and Km (TMDD-MM model) or using the experimental human values for kint, kdeg and KD (TDMM-QE model).

Prediction of human PK for different dose levels are performed in Simulx and the actual phase I PK data is then overlaid.

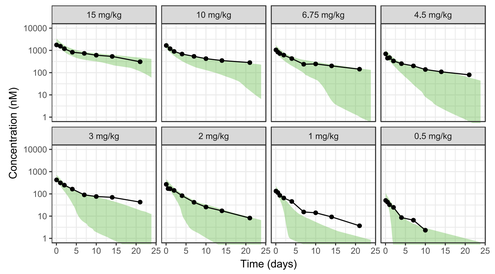
Parameter scaling

		2-cpt		TMDD MM		TMDD QE	
		Param	CV	Param	CV	Param	CV
V/F	Fixed to typical value for IgGs	40 mL/kg	15.2%	40 mL/kg	20.1%	40 mL/kg	17.3%
k	Allometric scaling $k_h = k_m\left(\frac{70}{4}\right)^{-0.25}$	0.105 /day	27.2%	0.069 /day	9.2%	0.075 /day	14.7%
k12	Allometric scaling $k_{12h} = k_{12,m}\left(\frac{70}{4}\right)^{-0.25}$	0.560 /day	54.3%	0.374 /day	10.8%	0.413 /day	20.4%
k21	Allometric scaling $k_{21,h} = k_{21,m}\left(\frac{70}{4}\right)^{-0.25}$	0.384 /day	20.0%	0.192 /day	12.6%	0.207 /day	15.6%
Vm	Assumed identical	-	-	34.7 nM/day	31.9%	-	-
Km	Assumed identical	-	-	12.3 nM	79.6%	-	-
R0	Assumed identical	-	-	-	-	1.27 nM	30.1%
kint	Fixed to experimental value	-	-	-	-	18 /day	-
kdeg	Fixed to experimental value	-	-	-	-	5 /day	37.3%
KD	Fixed to experimental value	-	-	-	-	2.9 nM	-

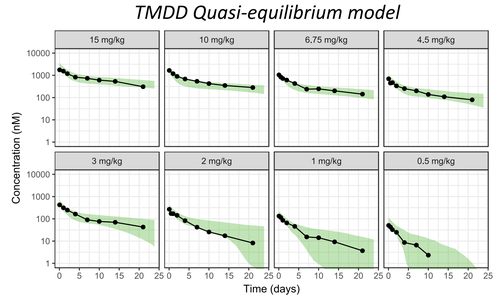
2-compartment model



TMDD Michaelis-Menten model



TMDD Quasi-equilibrium model



Only the TMDD QE model is able to correctly predict the human PK.

Prediction of human MABEL ('Minimal anticipated biological effect level')

The TMDD-QE model can be used to simulate the free target relative to baseline as a surrogate of the biological effect, in order to determine the MABEL.

This is possible only with the TMDD-QE model, as it is the only one to include the target as model variable.

In the absence of consensus MABEL definition, it is defined in this case study as a 10% decrease of free receptor at peak.

The MABEL is predicted to be around 0.005 mg/kg, well below the lowest dose tested in the first-in-human study.