Model-Informed Drug Development

MIDD+

2021 Virtual Conference

Using a population mechanistic TMDD model calibrated on preclinical monkey data to simulate first-in-human

Géraldine Ayral

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Challenges for First-in-human

Which dose to choose to elicit the desired effect (efficacy), without causing harm (safety)?

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No Observable Adverse Effect Level:

- Determine NOAEL dose in preclinical species
- Scale to human based on body-weight or BSA
- Add 10-fold safety margin

Not safe, because focuses on dose, not effect.

Challenges for First-in-human

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Minimal Anticipated Biological Effect Level:

- Requires to understand the PD (biological effect)
- PK/PD modeling can give valuable insight (e.g on receptor occupancy)

Challenges for First-in-human

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Minimal Anticipated Biological Effect Level:

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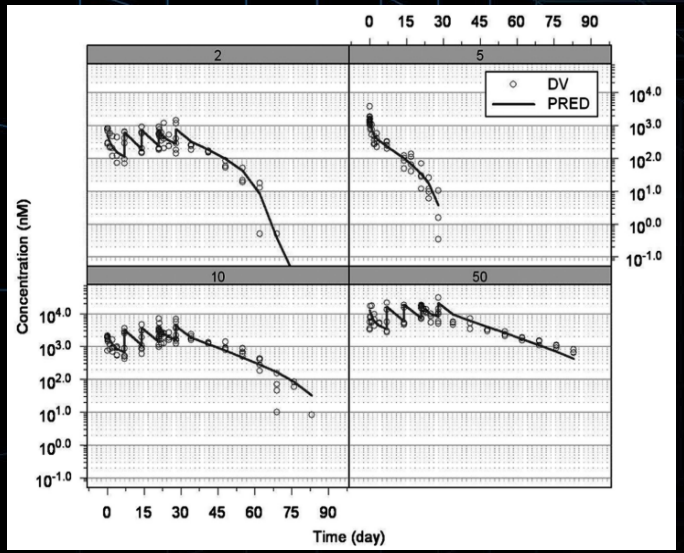
- PK/PD modeling can give valuable insight (e.g on receptor occupancy)

Can we accurately predict the human PK and PD to determine the MABEL using a model fitted on preclinical data?

Case study

Preclinical monkey PK

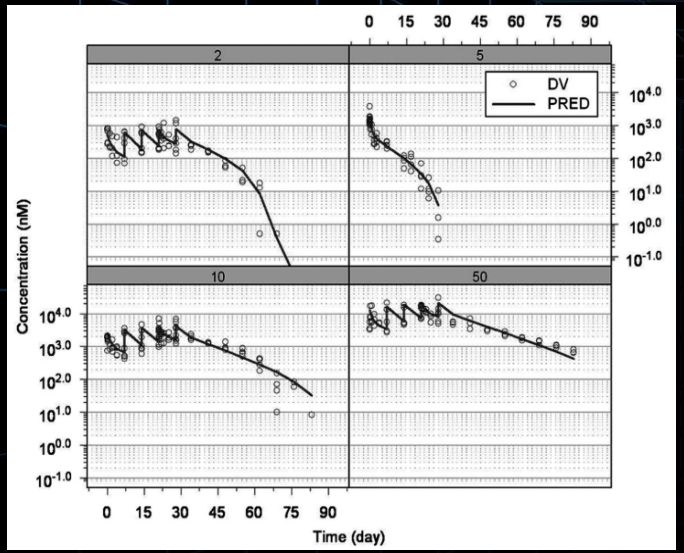


Luu KT et al. (2012). **A Model-Based Approach to Predicting the Human Pharmacokinetics of a Monoclonal Antibody Exhibiting Target-Mediated Drug Disposition.** *Journal of Pharmacology and Experimental Therapeutics*, *341*(3), 702–708.

- PF-03446962, an IgG2 antibody directed against human ALK1 receptor
- ALK1 is a cell surface type I receptor of the TGFβ receptor family expressed on endothelial cells as well as various solid tumors
- ALK1 has been proposed as an antiangiogenic target

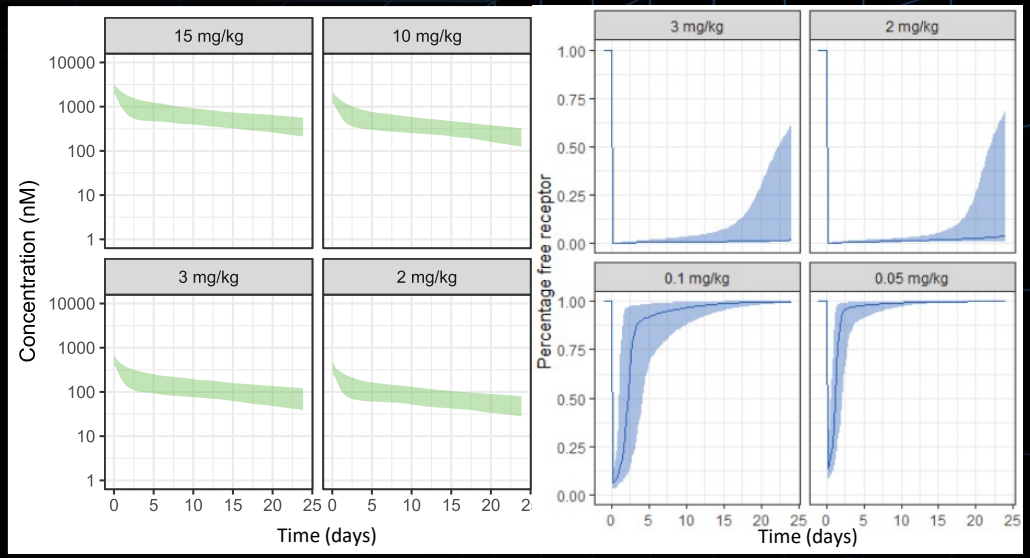
Challenges for First-in-human

Preclinical monkey PK



Accurate prediction possible?

Predicted human PK and PD



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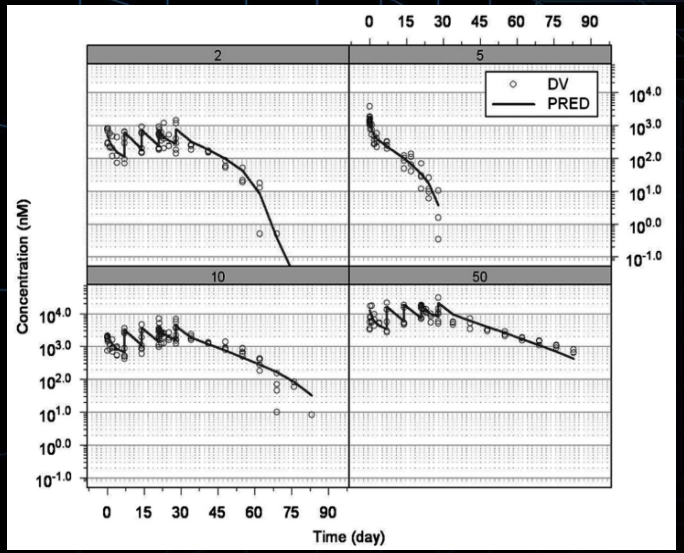
Challenges for First-in-human

Preclinical monkey PK



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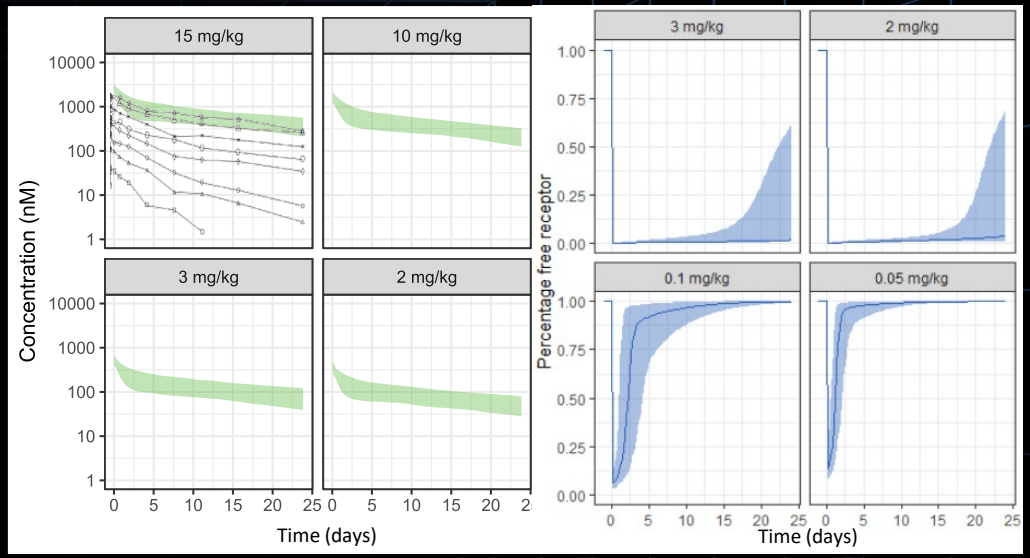
Accurate prediction possible?

Human PK and PD

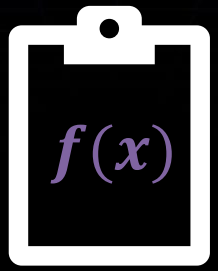


Goff LW et al. (2016) **A Phase I Study of the Anti-Activin Receptor-Like Kinase 1 (ALK-1) Monoclonal Antibody PF-03446962 in Patients with Advanced Solid Tumors**. *Clinical Cancer Research*, 22(9), 2146–2154.

Workflow

Monolix

Step 1:
Develop a popPK model to capture the monkey data



Step 2:
Scale the monkey parameters to human

Simulx

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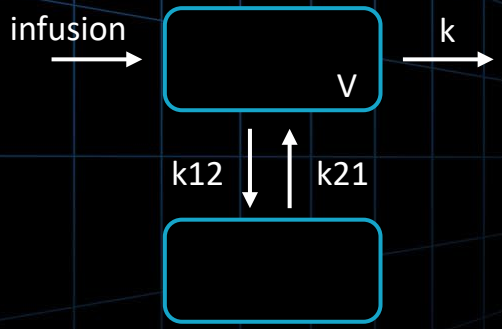
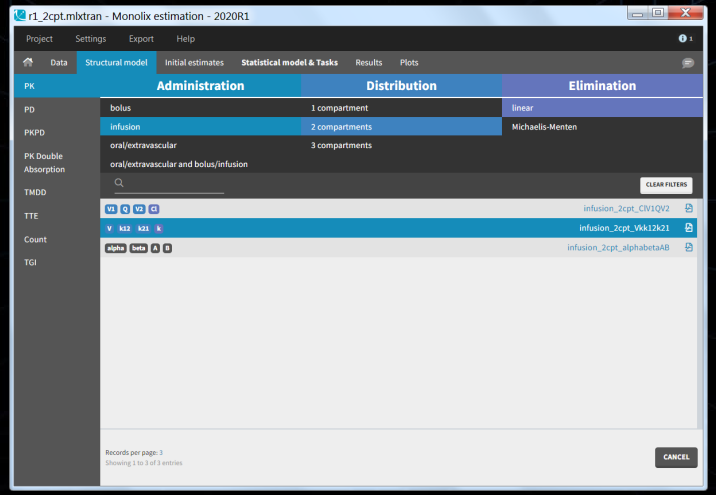
Step 1: Model development with Monolix

2-compartment model



Setup in Monolix GUI

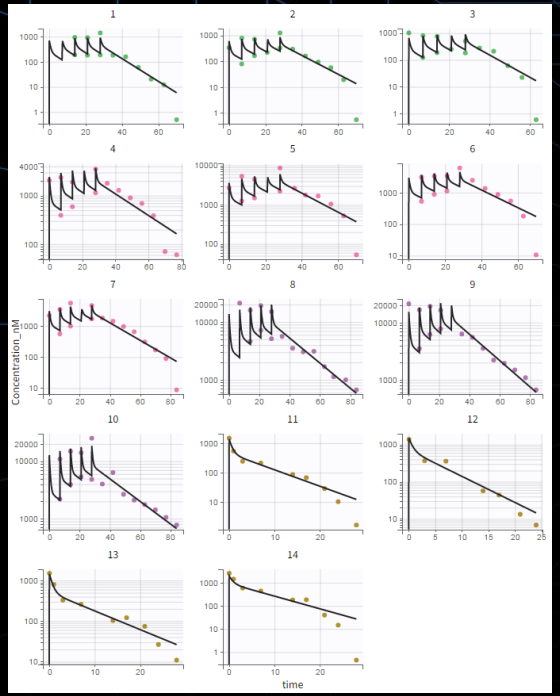


Estimated parameters

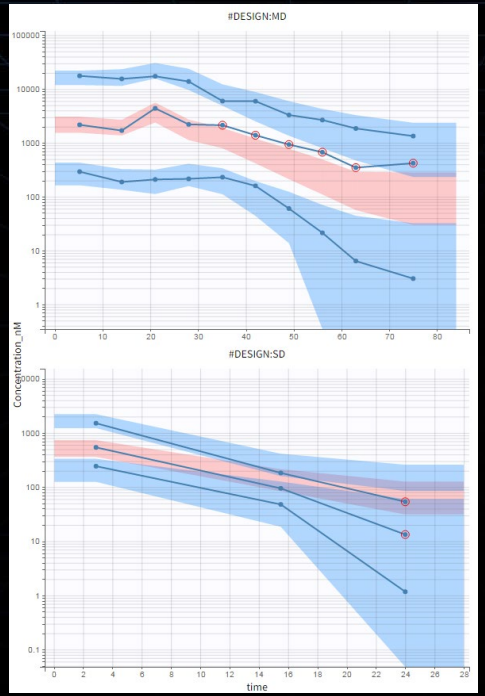
	Value	CV
V/F	22 mL/kg	17%
k	0.21 /day	29%
k12	0.80 /day	36%
k21	0.57 /day	30%

Step 1: Model development with Monolix

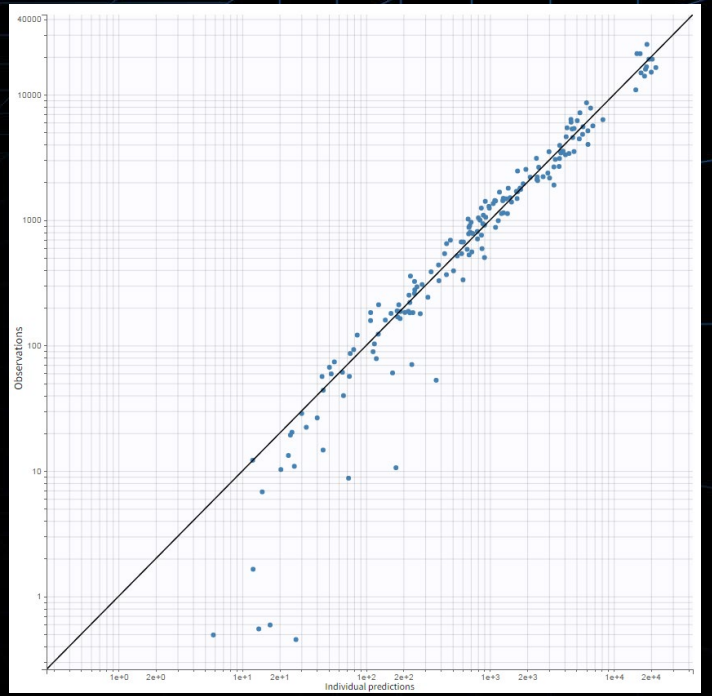
Individual fits



VPC (split by design)



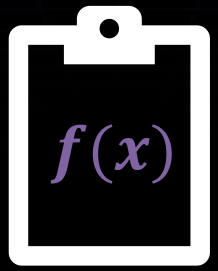
Obs versus Pred



Workflow

Monolix

Step 1:
Develop a popPK model to capture the monkey data



Step 2:
Scale the monkey parameters to human

Simulx

Step 3:
Predict the human PK and PD for various doses

Step 2: Parameter scaling to human

Monkey PK parameters are scaled using typical allometric scaling

	Monkey	CV				Human	CV
V/F	22 mL/kg	17%	=>	Fixed to typical value for IgGs	=>	40 mL/kg	17%
k	0.21 /day	29%	=>	Allometric scaling $k_h = k_m \left(\frac{70}{4}\right)^{-0.25}$	=>	0.10 /day	29%
k12	0.80 /day	36%	=>	Allometric scaling $k_{12,h} = k_{12,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.39 /day	36%
k21	0.57 /day	30%	=>	Allometric scaling $k_{21,h} = k_{21,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.28 /day	30%

$$CL_h = CL_m \left(\frac{BW_h}{BW_m}\right)^{0.75} \quad \text{and} \quad V_h = V_m \left(\frac{BW_h}{BW_m}\right)^{1} \quad \Rightarrow \quad k_h = \frac{CL_h}{V_h} = k_m \left(\frac{BW_h}{BW_m}\right)^{-0.25}$$

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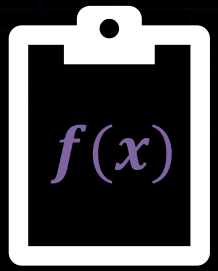

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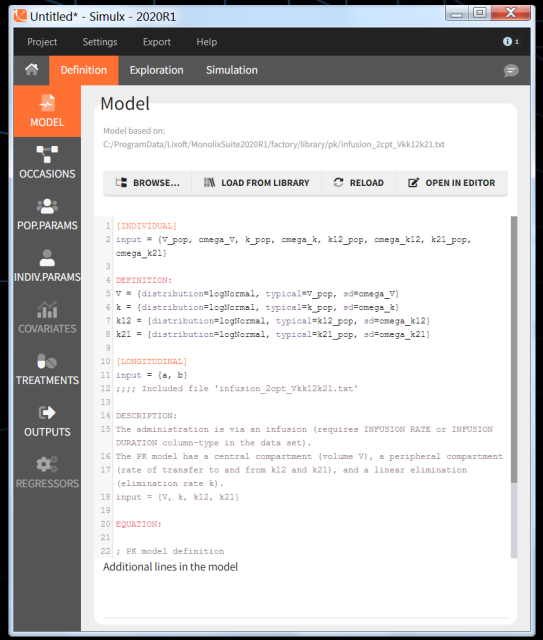
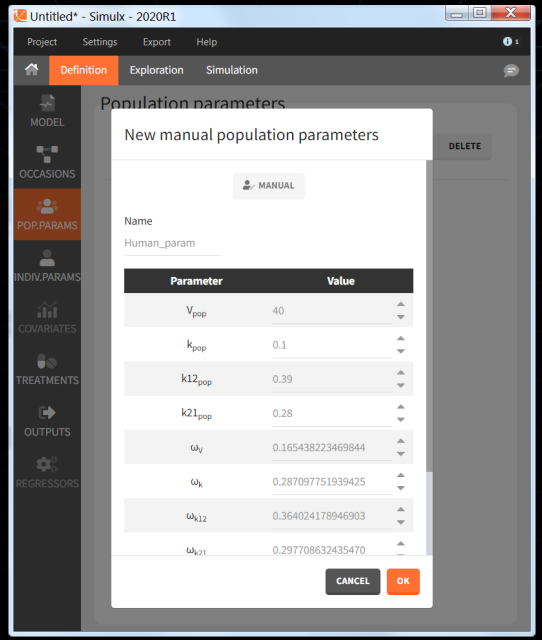
Step 3: FIH simulations with Simulx

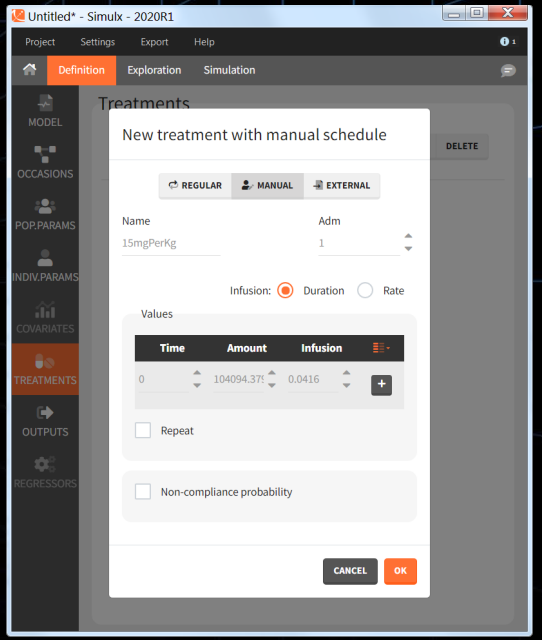
Import of Monolix run into Simulx



Modification of the pop parameters to represent human

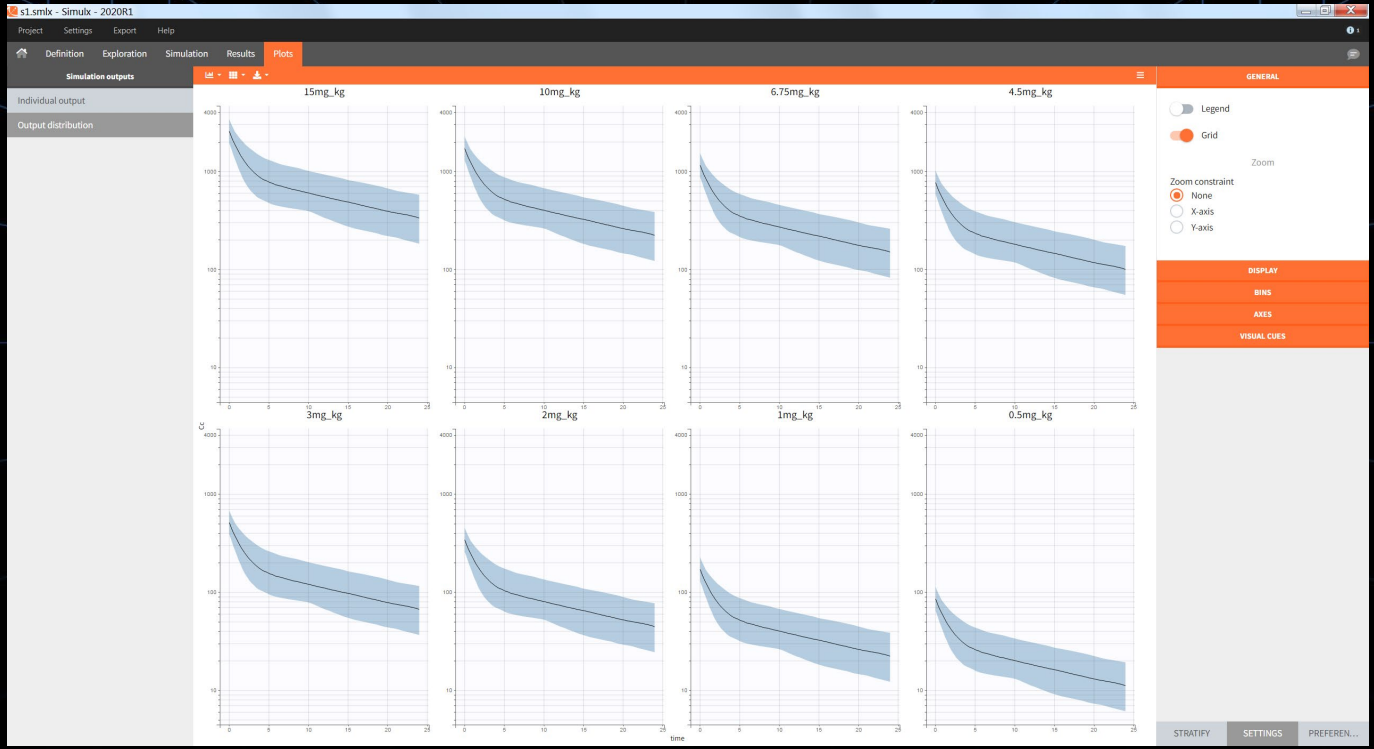


Definition of candidate FIH doses



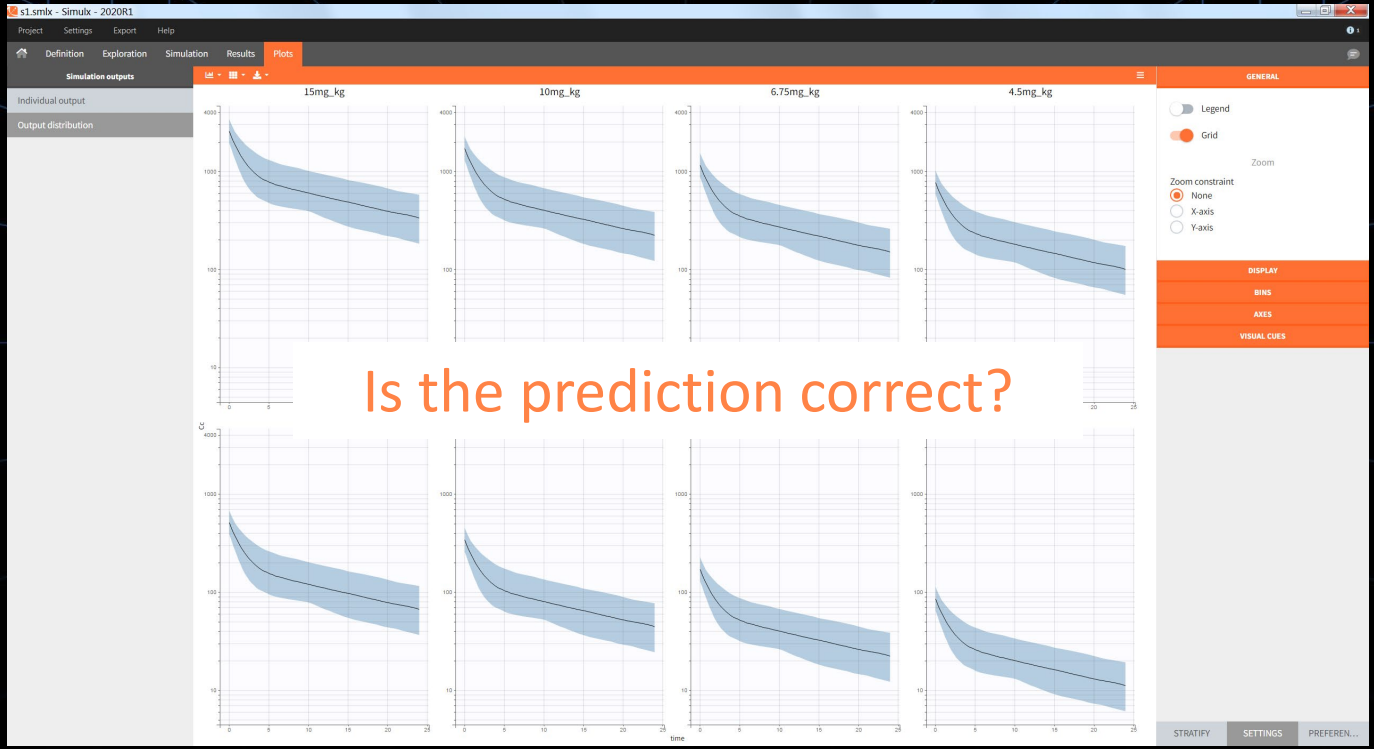
Step 3: FIH simulations with Simulx

Prediction of human PK for various dose levels



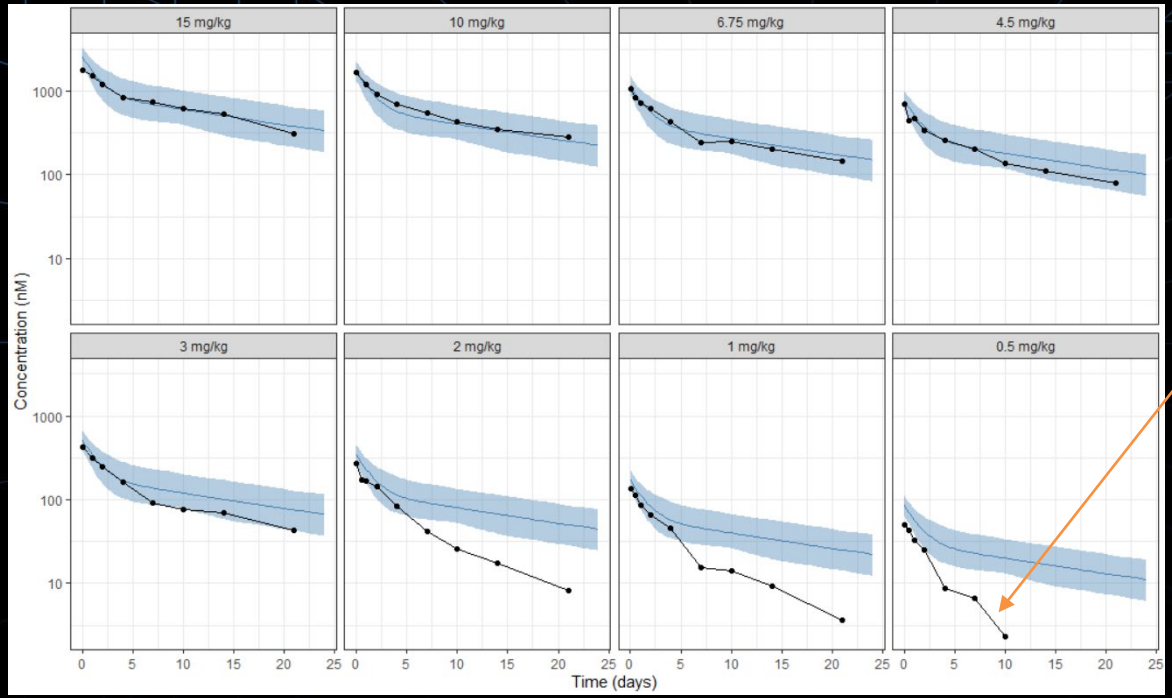
Step 3: FIH simulations with Simulx

Prediction of human PK for various dose levels

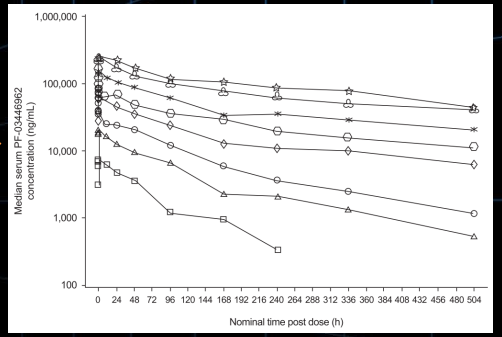


Step 3: FIH simulations with Simulx

Prediction of human PK overlaid with averaged phase I data



Phase I data (Goff et al. 2016)



Average over n=6 per group

Wrong prediction for the small doses.

Workflow

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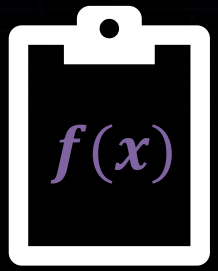

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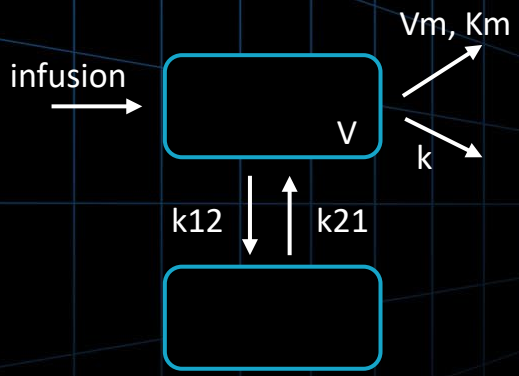
Step 1b: Model development with Monolix

MM TMDD model



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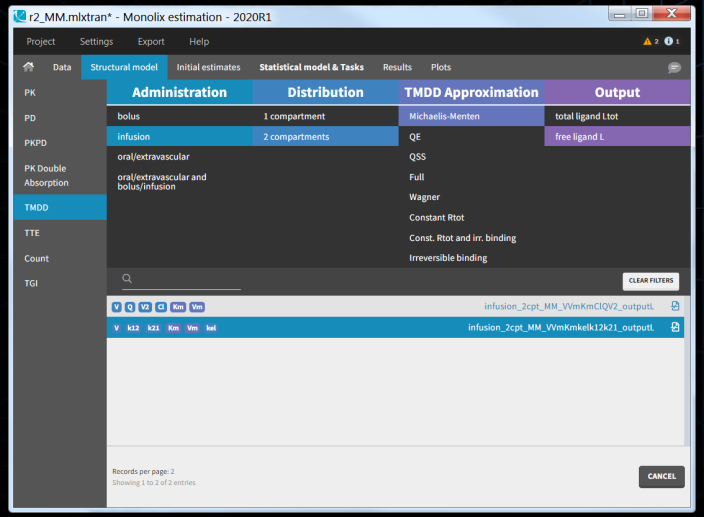

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	Value	CV
V/F	22 mL/kg	18%
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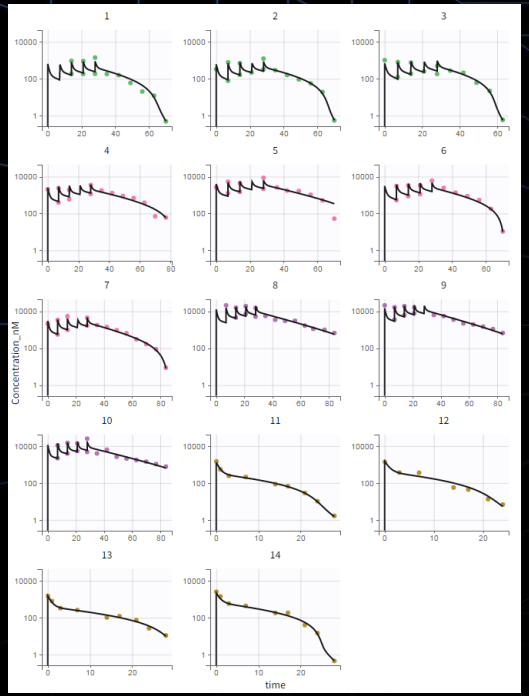
k12	0.79 /day	15%
k21	0.39 /day	11%
Vm	27 nM/day	42%
Km	3.5 nM	61%

Step 1b: Model development with Monolix

Individual fits



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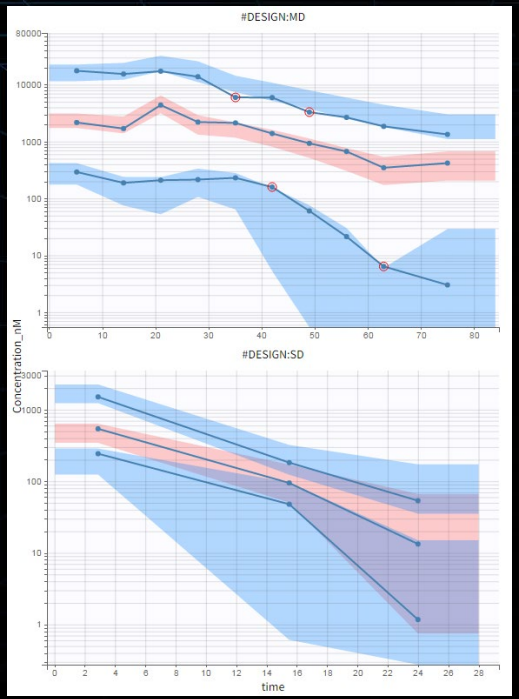

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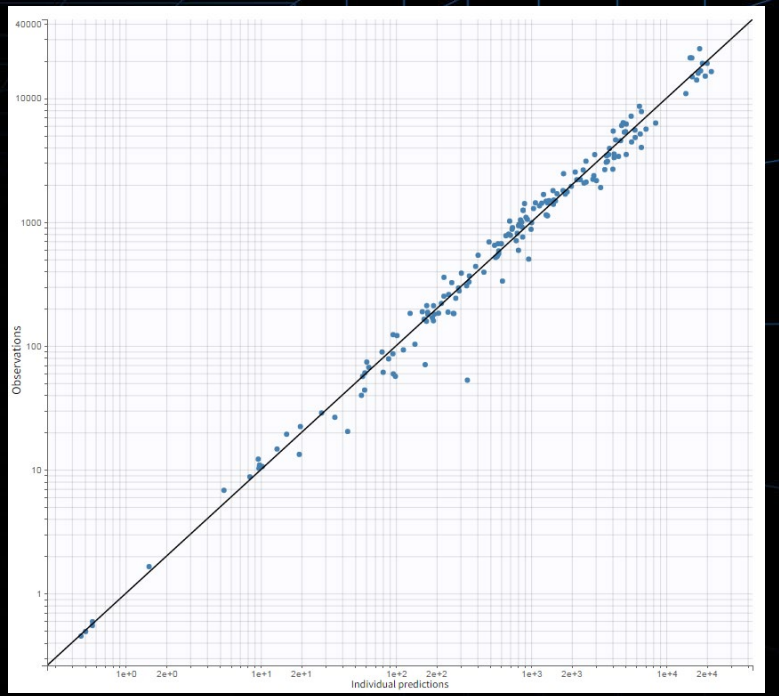

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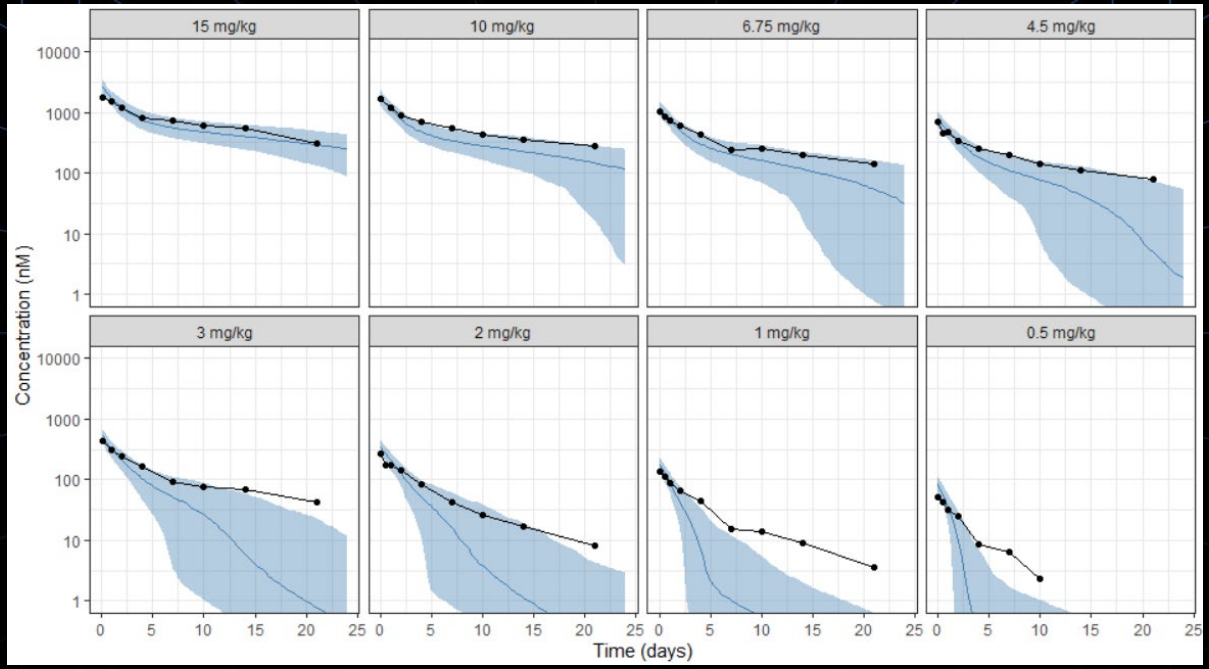
k21	0.39 /day	11%	=>	Allometric scaling $k_{21,h} = k_{21,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.19 /day	11%
Vm	27 nM/day	42%	=>	Assumed identical	=>	27 nM/day	42%
Km	3.5 nM	61%	=>	Assumed identical	=>	3.5 nM	61%

Step 3b: FIH simulations with Simulx

Prediction of human PK overlaid with averaged phase I data



Wrong prediction for the small doses.

Workflow

Monolix

Step 1:
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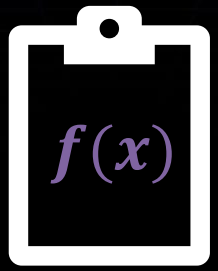

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Simulx

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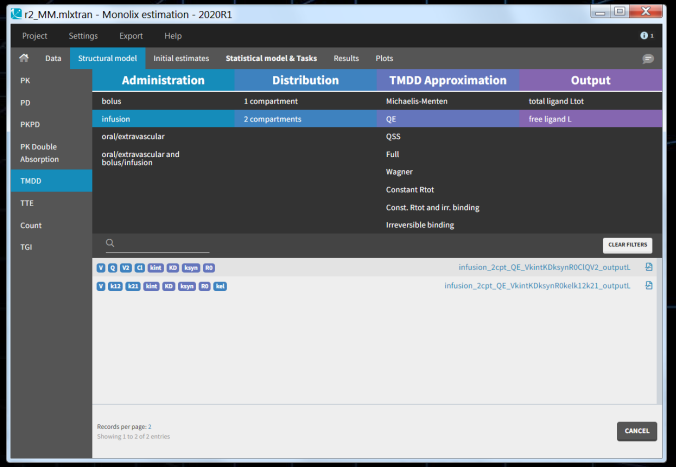
Step 1c: Model development with Monolix

Mechanistic model QE model

Setup in Monolix GUI



Step 1c: Model development with Monolix

Mechanistic model QE model

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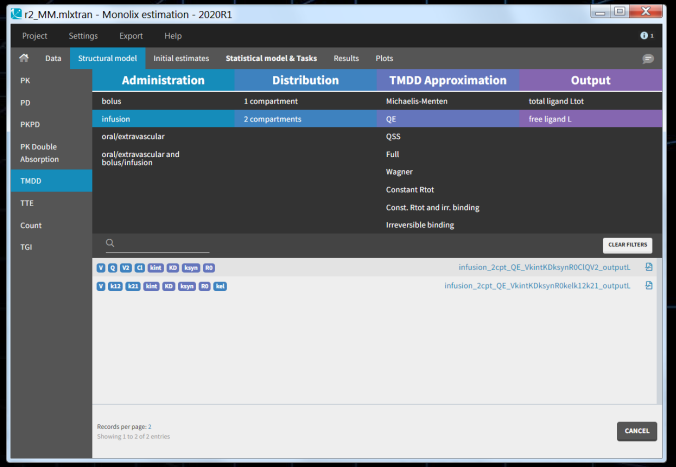
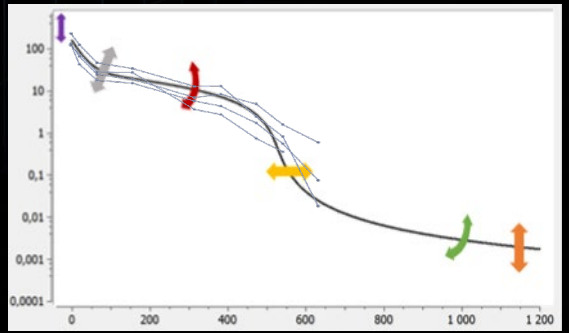




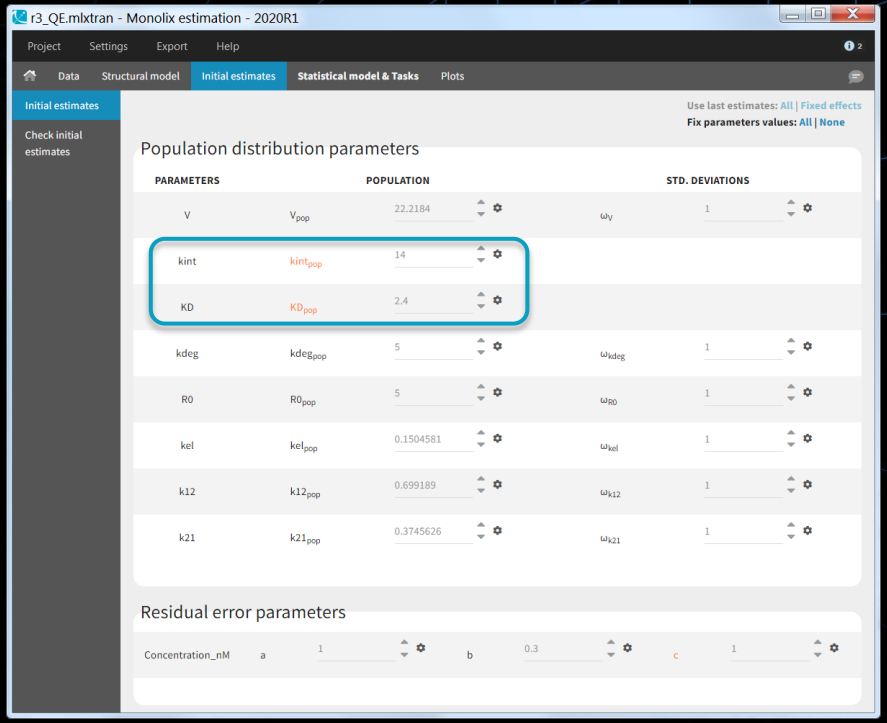
KD and kint are not identifiable from the data

Step 1c: Model development with Monolix

Literature values

	Monkey	Human	Experiment
kint	14 /day	18 /day	internalization via FACS
KD	2.4 nM	2.9 nM	surface plasmon resonance
kdeg	_	5 /day	decay via RNA expression

Setup in Monolix GUI



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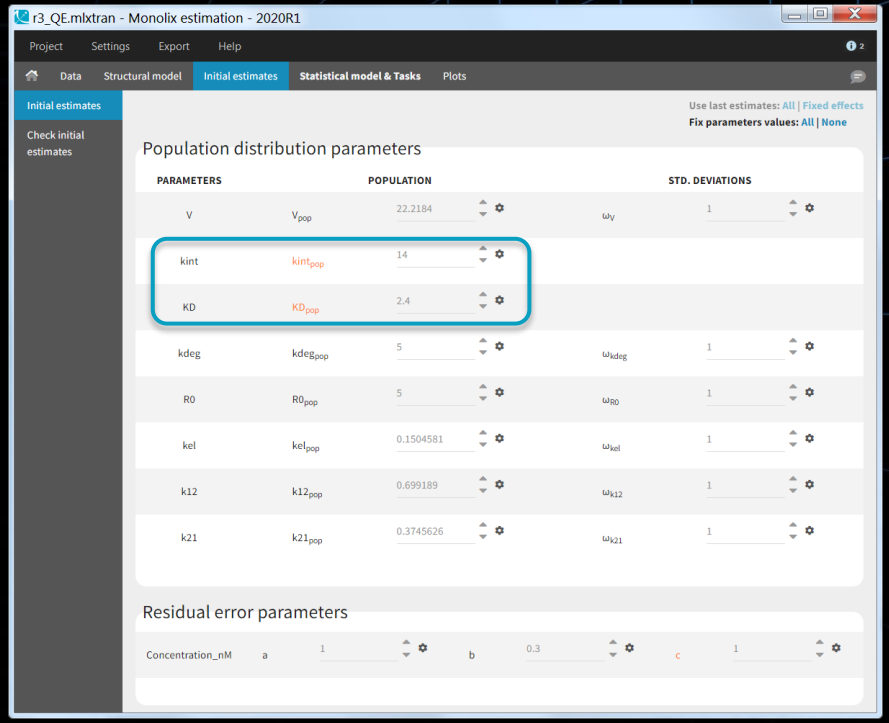
k	0.16 /day	30%
k12	0.88 /day	11%
k21	0.44 /day	10%
R0	1.8 nM	29%
kint	14 /day (fixed)	-
kdeg	13 /day	71%
KD	2.4 nM (fixed)	-

Setup in Monolix GUI



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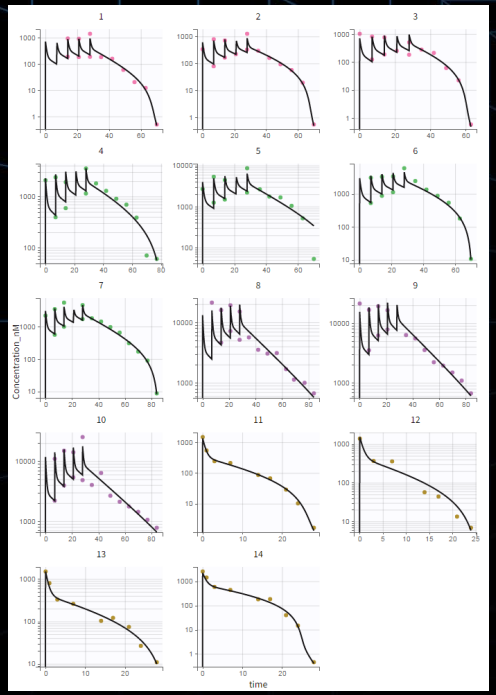
Step 1c: Model development with Monolix

Individual fits



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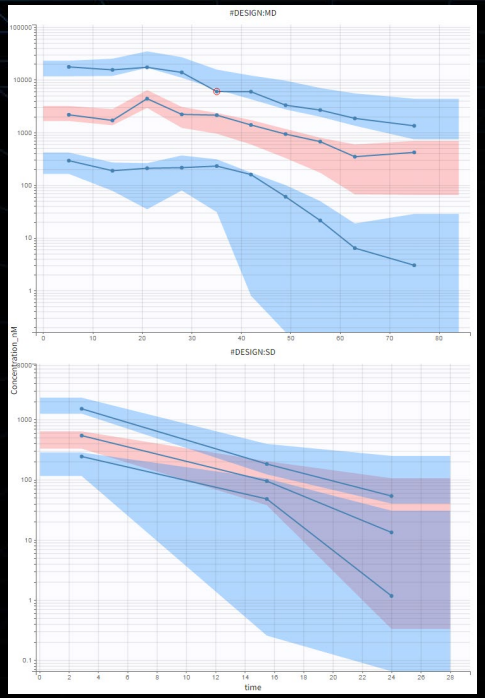

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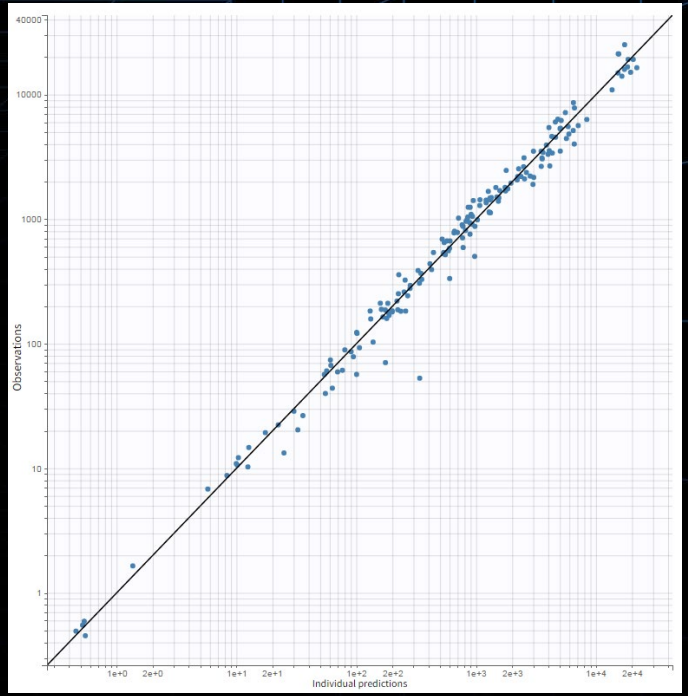


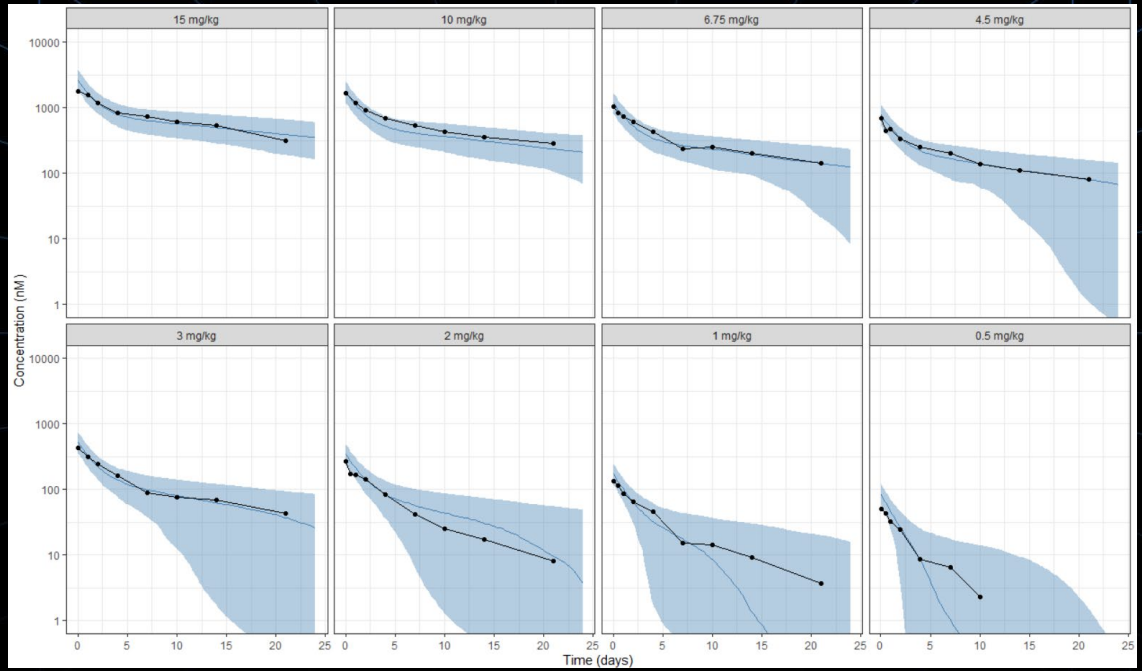
Step 2c: Parameter scaling to human

Monkey PK parameters are scaled using allometric scaling and literature values

	Monkey	CV				Human	CV
V/F	22 mL/kg	23%	=>	Fixed to typical value for IgGs	=>	40 mL/kg	23%
k	0.16 /day	30%	=>	Allometric scaling $k_h = k_m \left(\frac{70}{4}\right)^{-0.25}$	=>	0.078 /day	30%
k12	0.88 /day	11%	=>	Allometric scaling $k_{12h} = k_{12,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.43 /day	11%
k21	0.44 /day	10%	=>	Allometric scaling $k_{21,h} = k_{21,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.22 /day	10%
R0	1.8 nM	29%	=>	Assumed identical	=>	1.8 nM	29%
kint	14 /day (fixed)	-	=>	Fixed to experimental value	=>	18 /day	-
kdeg	13 /day	71%	=>	Fixed to experimental value	=>	5 /day	71%
KD	2.4 nM (fixed)	-	=>	Fixed to experimental value	=>	2.9 nM	-

Step 3c: FIH simulations with Simulx

Prediction of human PK overlaid with averaged phase I data



Correct prediction of all doses.

Step 3c: FIH simulations with Simulx

Prediction of free target relative to baseline (surrogate of the biological effect)

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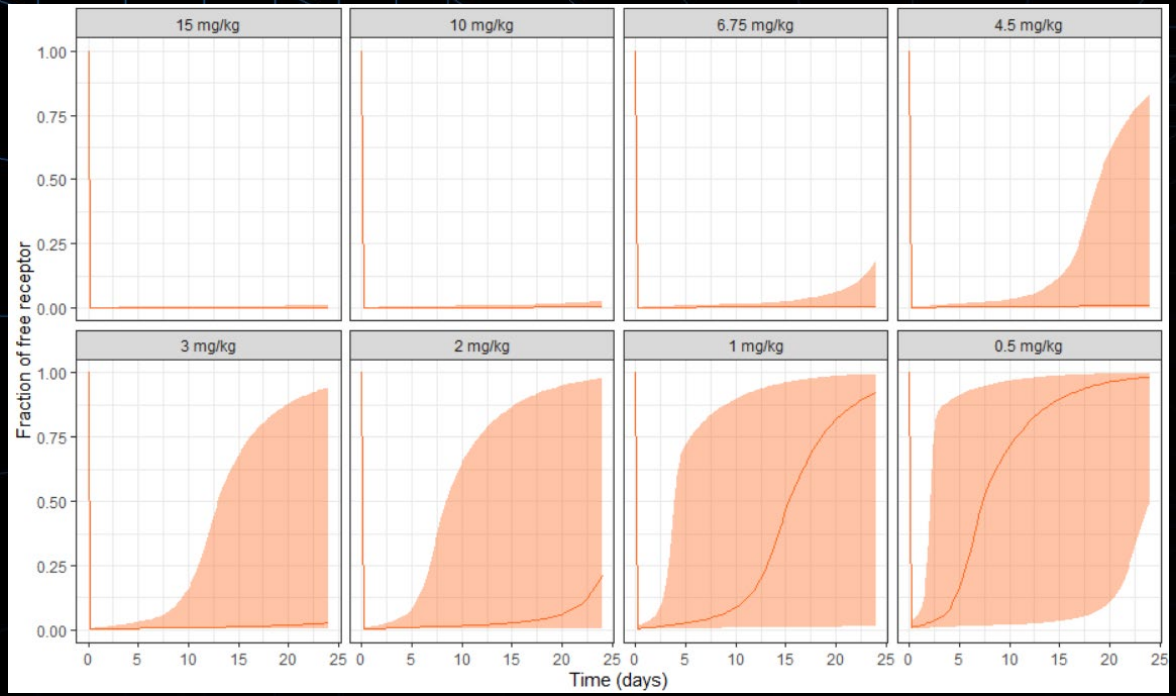
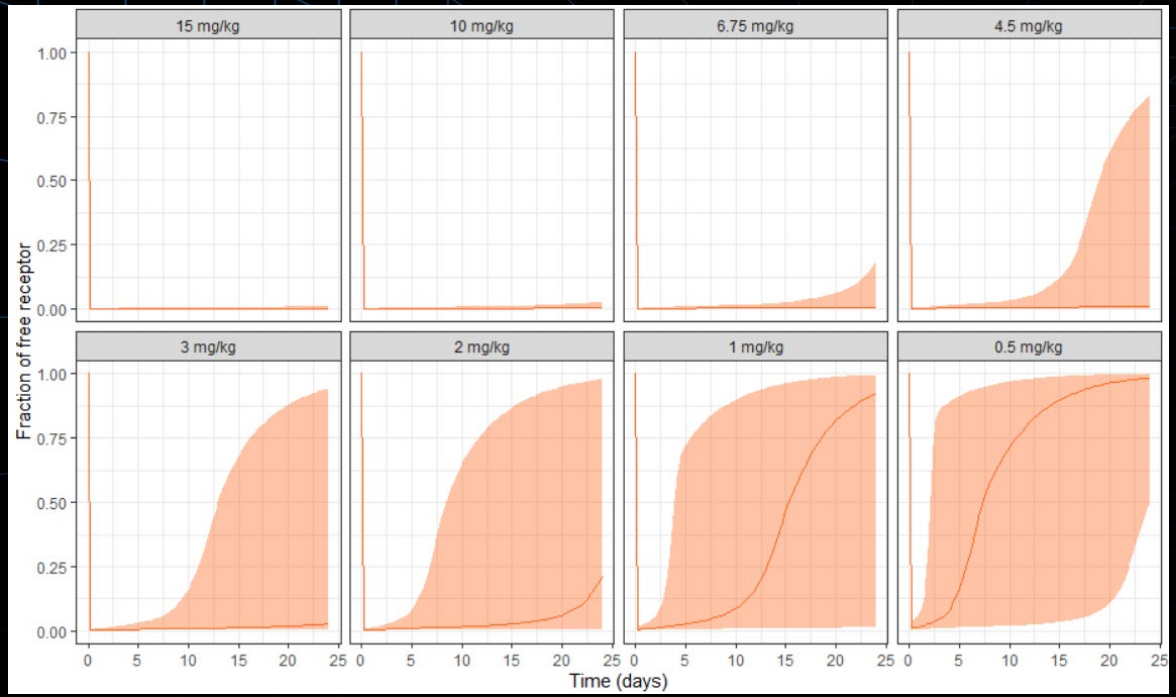
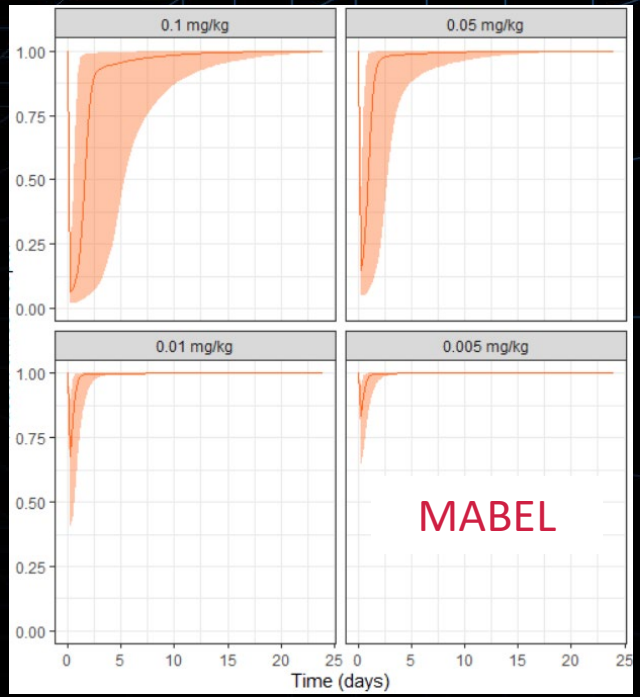
Prediction of free target relative to baseline (surrogate of the biological effect)



Step 3c: FIH simulations with Simulx

Prediction of free target relative to baseline (surrogate of the biological effect)





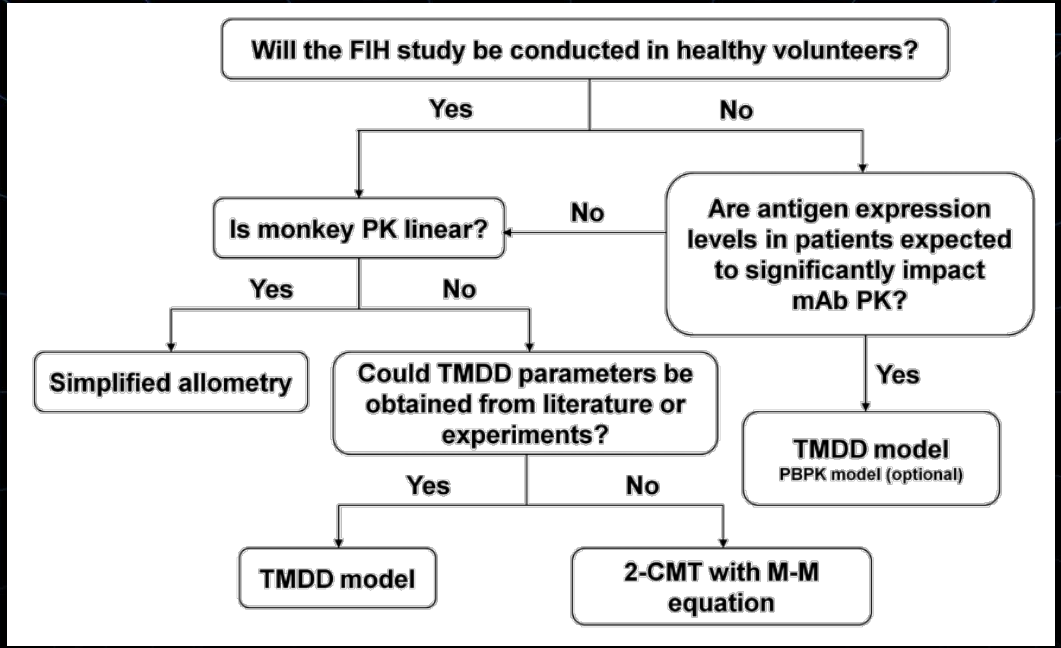
Overview

	2-cpt model	TMDD MM	TMDD QE with exp. value
Captures monkey PK	≈ (LL=2448)	✓ (LL=2360)	✓ (LL=2365)
Prediction of high doses (linear PK range)	✓	✓	✓
Prediction of low doses (nonlinear PK range)	✗	✗	✓
Prediction of target occupancy	✗	✗	✓

The choice of the model depends on the goal.

Which model to choose to predict the human PK (blindly)?

Guidelines



Wang J., Iyer S., Fielder P. J., Davis J. D., & Deng R. (2016). **Projecting human pharmacokinetics of monoclonal antibodies from nonclinical data: comparative evaluation of prediction approaches in early drug development**. *Biopharmaceutics & Drug Disposition*, *37*(2), 51–65.

Conclusion

- A mechanistic TMDD model with:
  - linear PK parameters allometrically scaled based on preclinical monkey PK data
  - TMDD parameters fixed to experimentally measured values

successfully predicts the human PK of PF-03446962.

- This model can be used to simulate target occupancy to determine the MABEL and guide the choice of the first-in-human dose.

Q&A

Questions & Answers

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