### Model-Informed Drug Development

## **2021 Virtual Conference**



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

Géraldine Ayral



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





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

#### No Observable Adverse Effect Level:

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

### Not safe, because focuses on dose, not effect.



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

#### No Observable Adverse Effect Level:

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- Scale to human based on bodyweight or BSA
- Add 10-fold safety margin

#### Minimal Anticipated Biological Effect Level:

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





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

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### Minimal Anticipated Biological Effect Level:

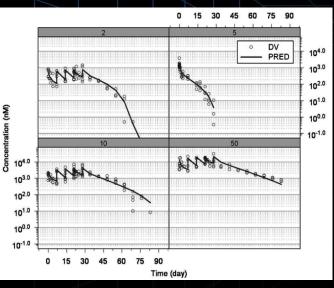
- Requires to understand the PD (biological effect)
- PK/PD modeling can give valuable insight (e.g on receptor occupancy)

### 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



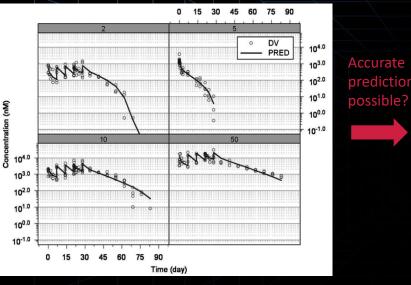
Luu KT et al. (2012). A Model-Based Approach to Predicting the Human Pharmacokinetics of a Monoclonal Antibody Exhibiting Target-Mediated Drug Disposition. *Journal of Pharmacology and Experimental Therapeutics*, *341*(3), 702–708.

- 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



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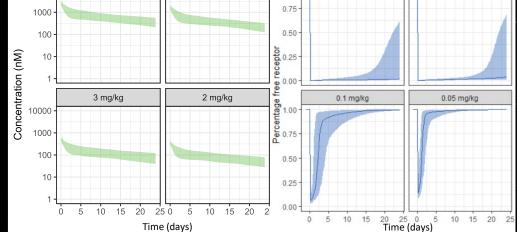
#### Preclinical monkey PK



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.



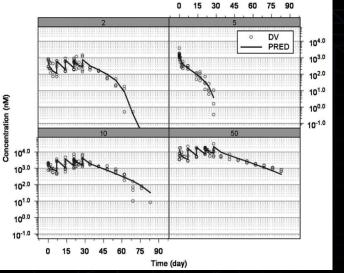






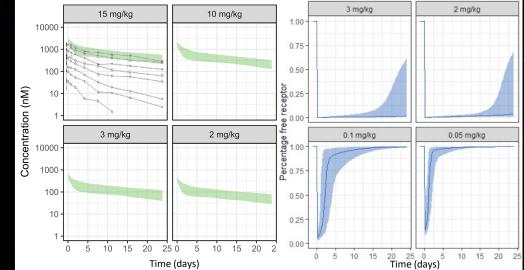
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#### Preclinical monkey PK



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.

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.

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## Workflow

### Monolix

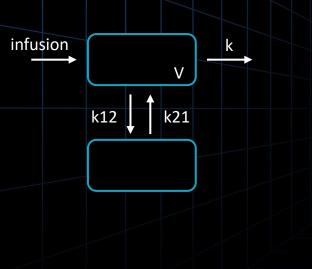


Step 1: Develop a popPK model to capture the monkey data Step 2: Scale the monkey parameters to human Step 3: Predict the human PK and PD for various doses

Simulx



#### 2-compartment model



#### Setup in Monolix GUI

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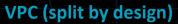
#### **Estimated parameters**

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

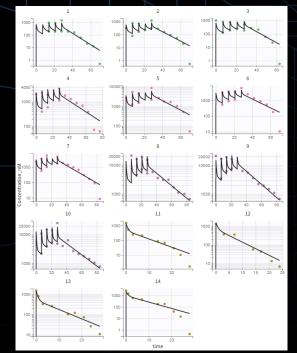


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Individual fits

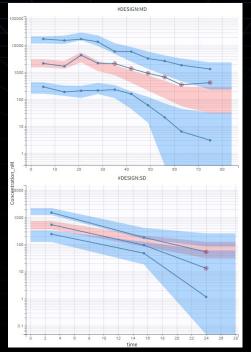


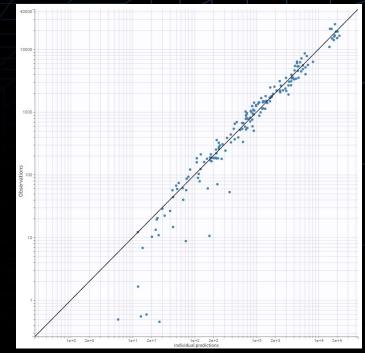
#### **Obs versus Pred**



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### Workflow

### Monolix



Step 1: Develop a popPK model to capture the monkey data Step 2: Scale the monkey parameters to human Step 3: Predict the human PK and PD for various doses

Simulx





## **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	$m\left(\frac{B}{B}\right)$	$\left(\frac{W_h}{W_h}\right)^{0.75}$	and		$V_h = V_m \left(\frac{BW_h}{BW}\right)^1$	k <sub>h</sub>	$= \frac{CL_h}{2}$	= km	$\left(\underline{BW_h}\right)^{-0}$
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 $CL_h$ 

## Workflow

### Monolix



Step 1: Develop a popPK model to capture the monkey data Step 2: Scale the monkey parameters to human Step 3: Predict the human PK and PD for various doses

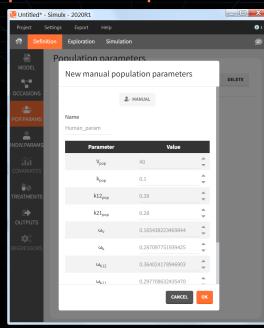
Simulx



#### Import of Monolix run into Simulx

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	cmega_k21} 3 4 DEFINITION: 5 V = (distribution=logNormal, typical=V_pop, sd=cmega_V)	
COVARIATES	<pre>k = (istributio=logicmal, typical=k2l_pop, sd=cmag_k) k12 = (istributio=logicmal, typical=k2l_pop, sd=cmag_k12) k21 = (istributio=logicmal, typical=k2l_pop, sd=cmag_k2l) (LAMOSTUDEIRAL)</pre>	
TREATMENTS	11 input = {e, b} 12 ;;;; Included file 'infusion_2cpt_Vkkl2k21.txt' 13	
	14 DESCRIPTION: 15 The administration is via an infusion (requires INFUSION RATE or INFUSION DURATION column-type in the data set).	
CEGRESSORS	<pre>16 The FK model has a central comparisent (values V), a peripheral comparisent 17 (rate of transfer to and from k12 and k21), and a linear elimination (elimination rate k). 18 input = (v, k, k12, k21) 19 20 EQUATION: 21 / FK model definition</pre>	
	Additional lines in the model	

### Modification of the pop parameters to represent human

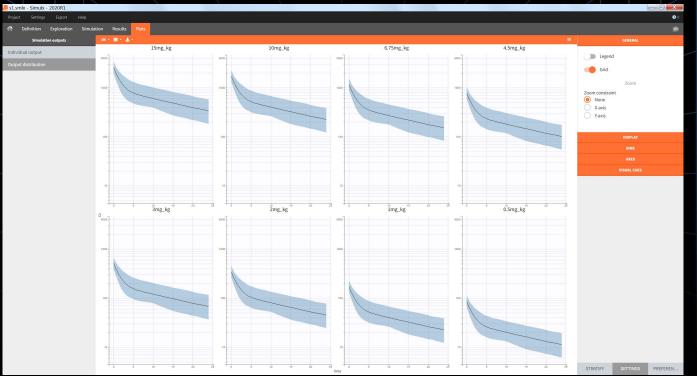


#### Definition of candidate FIH doses

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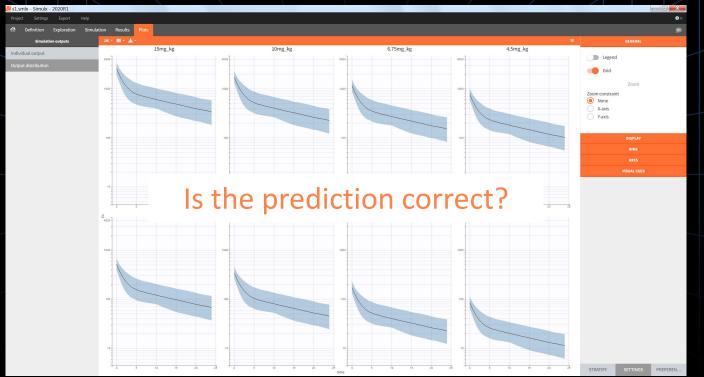
#### Prediction of human PK for various dose levels





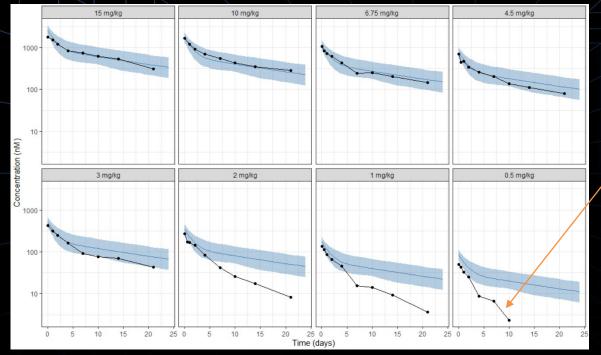


#### Prediction of human PK for various dose levels

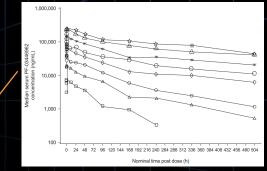




#### Prediction of human PK overlaid with averaged phase I data



#### Phase I data (Goff et al. 2016)



Average over n=6 per group

# Wrong prediction for the small doses.





### Workflow

### Monolix

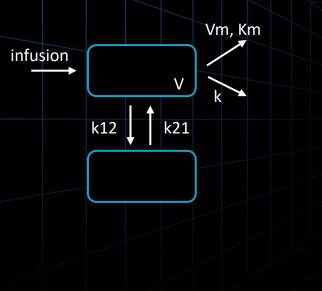


Step 1: Develop a popPK model to capture the monkey data Step 2: Scale the monkey parameters to human Step 3: Predict the human PK and PD for various doses

Simulx



#### MM TMDD model



#### **Setup in Monolix GUI**

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		infusion		2 compartments			free ligand L	
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#### **Estimated parameters**

	Value	CV
V/F	22 mL/kg	18%
k	0.15 /day	14%
k12	0.79 /day	15%
k21	0.39 /day	11%
Vm	27 nM/day	42%
Km	3.5 nM	61%

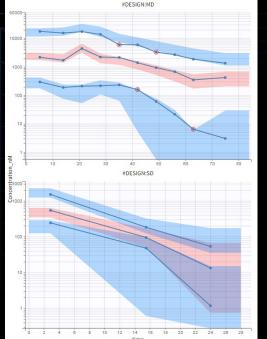


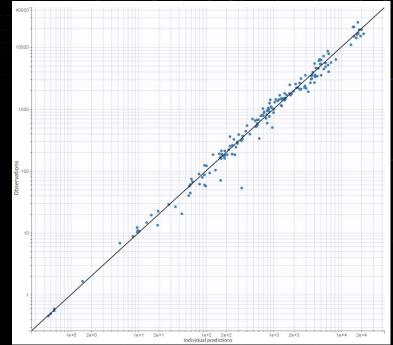
**Individual fits** 

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### VPC (split by design)





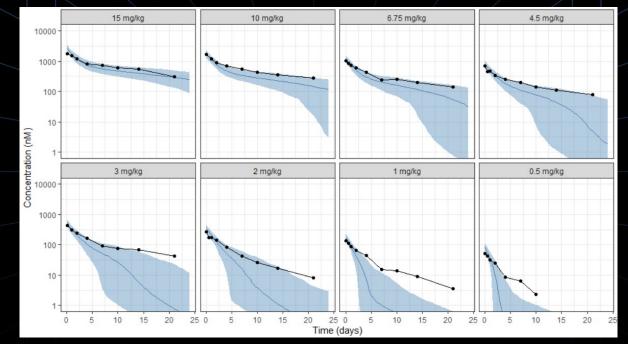
**Obs versus Pred** 



## **Step 2b:** Parameter scaling to human

#### Monkey PK parameters are scaled using typical allometric scaling

	Monkey	CV				Human	CV
V/F	22 mL/kg	18%	=>	Fixed to typical value for IgGs	=>	40 mL/kg	18%
k	0.15 /day	14%	=>	Allometric scaling $k_h = k_m \left(rac{70}{4} ight)^{-0.25}$	=>	0.073 /day	14%
k12	0.79 /day	15%	=>	Allometric scaling $k_{12h} = k_{12,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.39 /day	15%
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%



#### Prediction of human PK overlaid with averaged phase I data

Wrong prediction for the small doses.





## Workflow

### Monolix

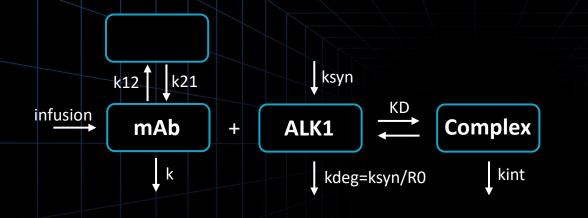


Step 1: Develop a popPK model to capture the monkey data Step 2: Scale the monkey parameters to human Step 3: Predict the human PK and PD for various doses

Simulx



#### Mechanistic model QE model



#### Setup in Monolix GUI

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	bolus	1 compartment	Michaelis-Menten	total ligand Ltot
РКРО	infusion	2 compartments	QE	free ligand L
PK Double	oral/extravascular		QSS	
Absorption	oral/extravascular and bolus/infusion		Full	
			Wagner	
			Constant Rtot	
			Const. Rtot and irr. binding	
			Irreversible binding	
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#### Mechanistic model QE model

#### Setup in Monolix GUI



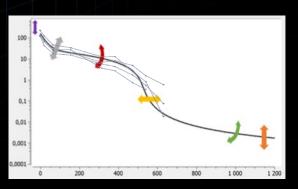
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	bolus	1 compartment	Michaelis-Menten	total ligand Ltot
	infusion	2 compartments	QE	free ligand L
PK Double	oral/extravascular		QSS	
Absorption	oral/extravascular and bolus/infusion		Full	
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### KD and kint are not identifiable from the data





#### 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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#### 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

#### **Estimated parameters**

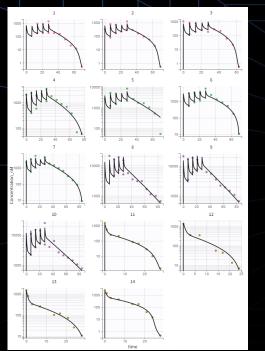
	Value	CV
V/F	22 mL/kg	23%
k	0.16 /day	30%
k12	0.88 /day	11%
k21	0.44 /day	10%
RO	1.8 nM	29%
kint	14 /day (fixed)	-
kdeg	13 /day	71%
KD	2.4 nM (fixed)	-

### Setup in Monolix GUI

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**Individual fits** 

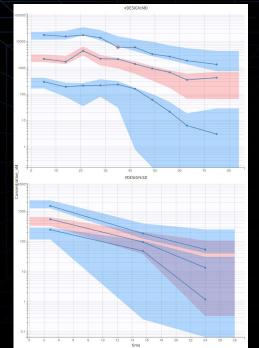


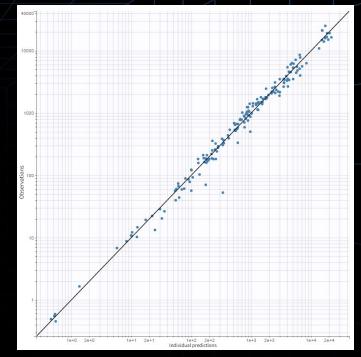
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### VPC (split by design)

**Obs versus Pred** 



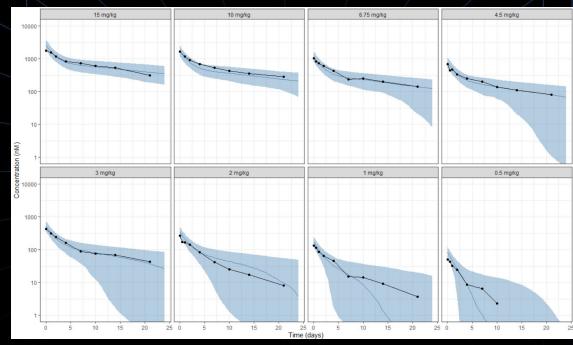


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## **Step 2c:** Parameter scaling to human

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%
RO	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	-



#### Prediction of human PK overlaid with averaged phase I data

**Correct prediction of all doses.** 





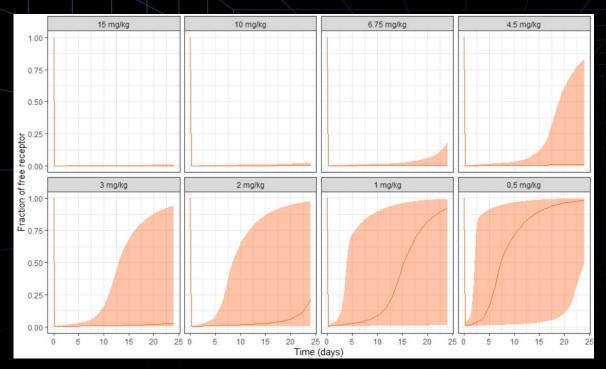
Prediction of free target relative to baseline (surrogate of the biological effect)





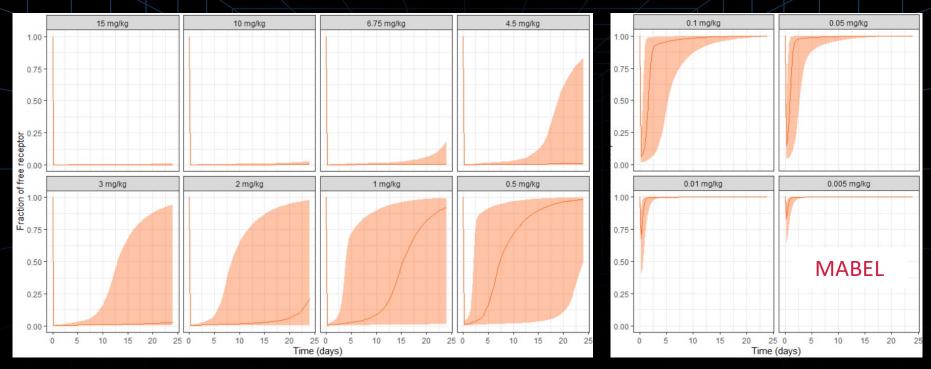


Prediction of free target relative to baseline (surrogate of the biological effect)





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	<b>≈</b> (LL=2448)	✓ (LL=2360)	✓ (LL=2365)
Prediction of high doses (linear PK range)	$\checkmark$	$\checkmark$	$\checkmark$
Prediction of low doses (nonlinear PK range)	×	×	$\checkmark$
Prediction of target occupancy	×	×	$\checkmark$

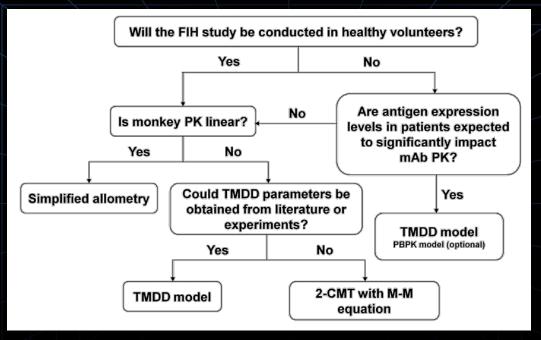
The choice of the model depends on the goal.

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:

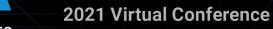
- Inear PK parameters allometrically scaled based on preclinical monkey PK data
- TMDD parameters fixed to experimentally measured values

### 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.



Model-Informed Drug Development



**Questions & Answers** 

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