



From phase I data to phase II trial design

Simulation and extension of a population PK model with
the MonolixSuite

Pauline Traynard

- Phase II clinical trials are often expensive and time consuming
 - Accelerate drug development with in silico simulations

- The development of pharmacokinetic/pharmacodynamic models and their simulation with predictive tools can
 - Help analyse phase I data to understand the drug ADME
 - Inform the design of subsequent clinical trials

- Example of phase I study
 - Goal: assess safety and tolerance of vanoxerine (GBR 12909)
 - PK and ECG measurements in 15 healthy patients

- Vanoxerine = dopamine reuptake inhibitor
 - researched for use in treating cocaine dependence

- Phase I study

NIDA-CPU-0002 Safety of GBR 12909 in cocaine experienced volunteers. April, 2002

- Goal: assess safety and tolerance of GBR 12909
- 15 healthy patients
- Oral doses: MD during 11 days
 - 0mg (3 patients)
 - 50mg (6 patients)
 - 75mg (6 patients)
- PK measurements
- ECG measurements in 15 healthy patients: QT interval, RR interval



1. Graphical exploration of the phase I data with Datxplore



2. Analyse the data with NCA and CA in Pkanalix

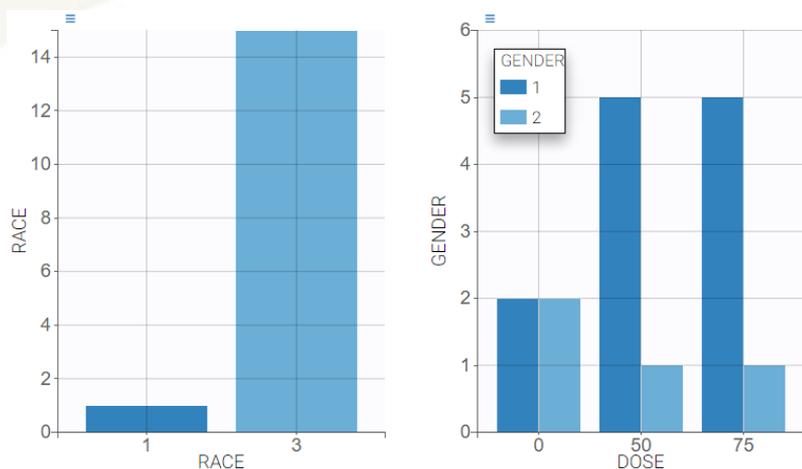


3. Develop a popPK/PD model with Monolix



4. Simulate different situations to inform phase II trial design

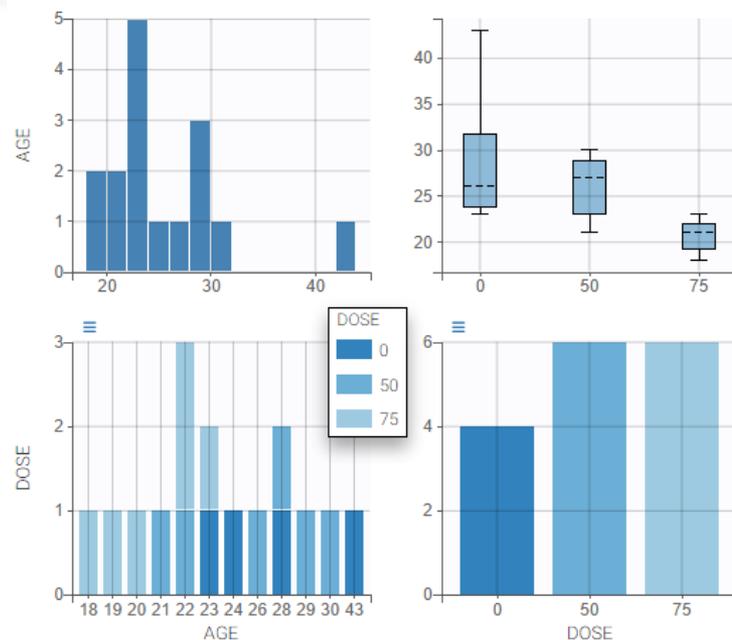
Straightforward data exploration with graphical visualization is useful to identify outliers and check the covariates



Identify covariates with not enough data

RACE: 1 individual in category 1

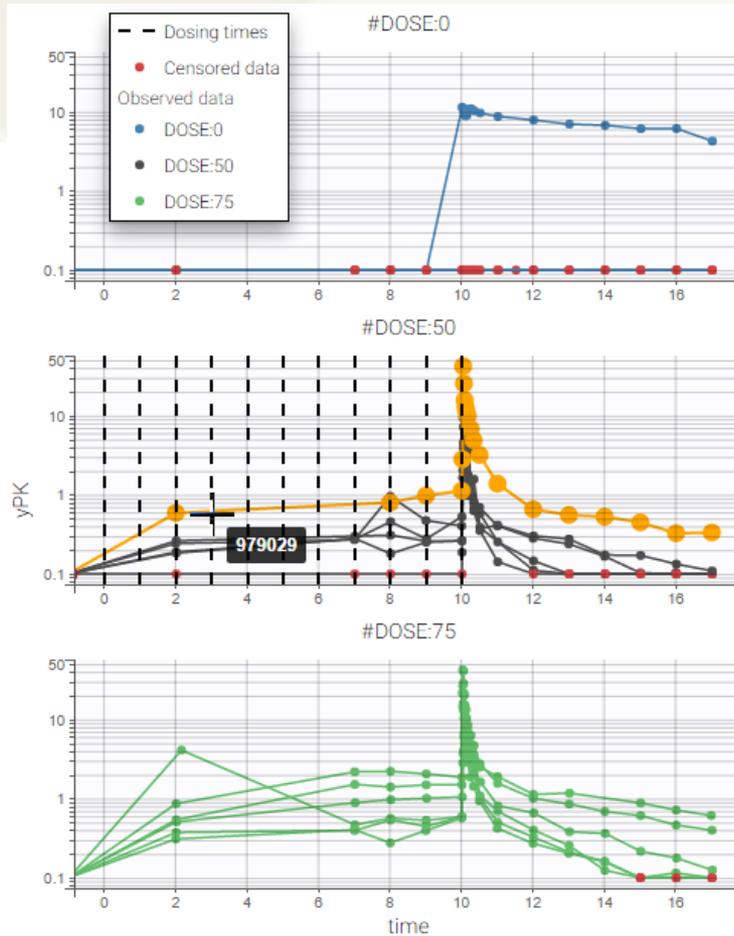
GENDER: 1 individual in category 2 for each treatment



Identify correlations

AGE is correlated with DOSE, and has an outlier

16 patients with 4 placebo, and BLQ values:



- One outlier in Placebo group
- Censored data with LOQ=0.1 are coherent



1. Graphical exploration of the phase I data with Datxplore



2. **Analyse the data with NCA and CA in Pkanalix**



3. Develop a popPK/PD model with Monolix

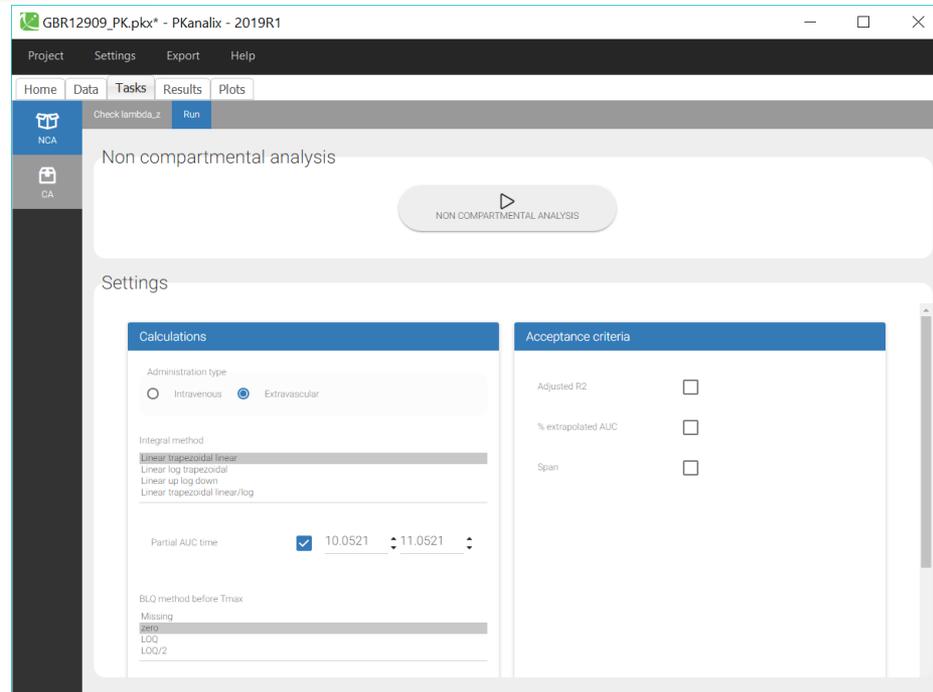
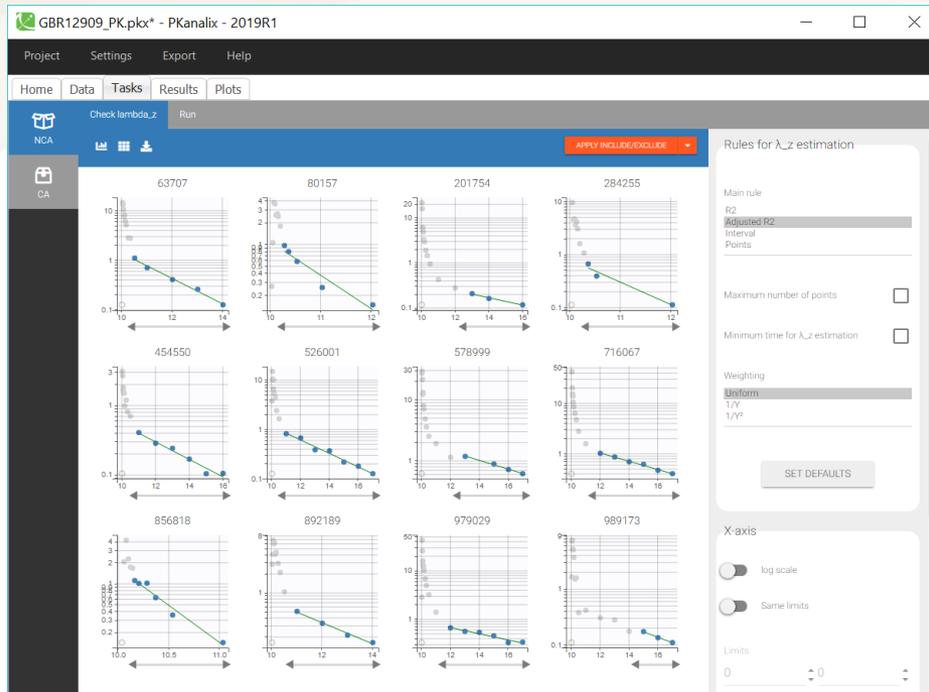


4. Simulate different situations to inform phase II trial design

PKAnalix: NCA



Straightforward NCA



Compute PK parameters

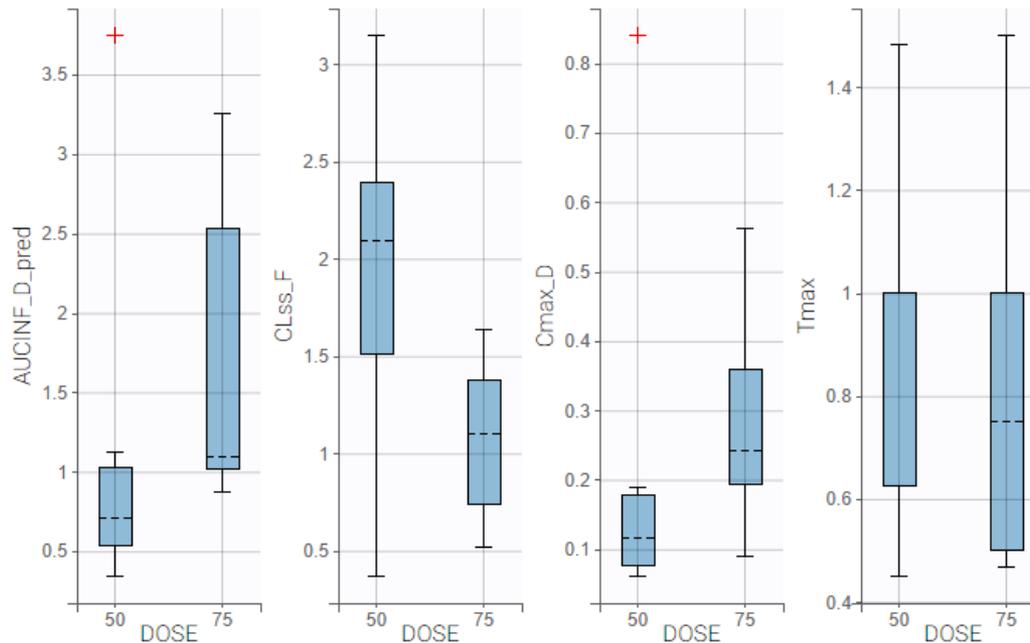
Coherent results with previous PK studies for GBR 12909 in humans that indicate :

1. An elimination half-life of about 48 hours (*Sogaard et al.*, 1990).
2. A rapid absorption with a mean Tmax of less than 1.5 hours (NIDACommunication, 2001).

	MIN	MAX	MEAN	SD
CAVG_0_24 (mg/L)	1.35	13.96	5.62	4.28
CLss_F (/h/L)	0.369	3.15	1.5	0.836
Cmax (mg/L)	3.06	42.2	16.51	14.19
HL_Lambda_z (h)	6.8	113.09	57.16	35.91
Rsq_adjusted	0.899	0.991	0.963	0.0322
Tmax since last dose (h)	0.45	1.5	0.867	0.382

Check correlations between PK parameters and covariates

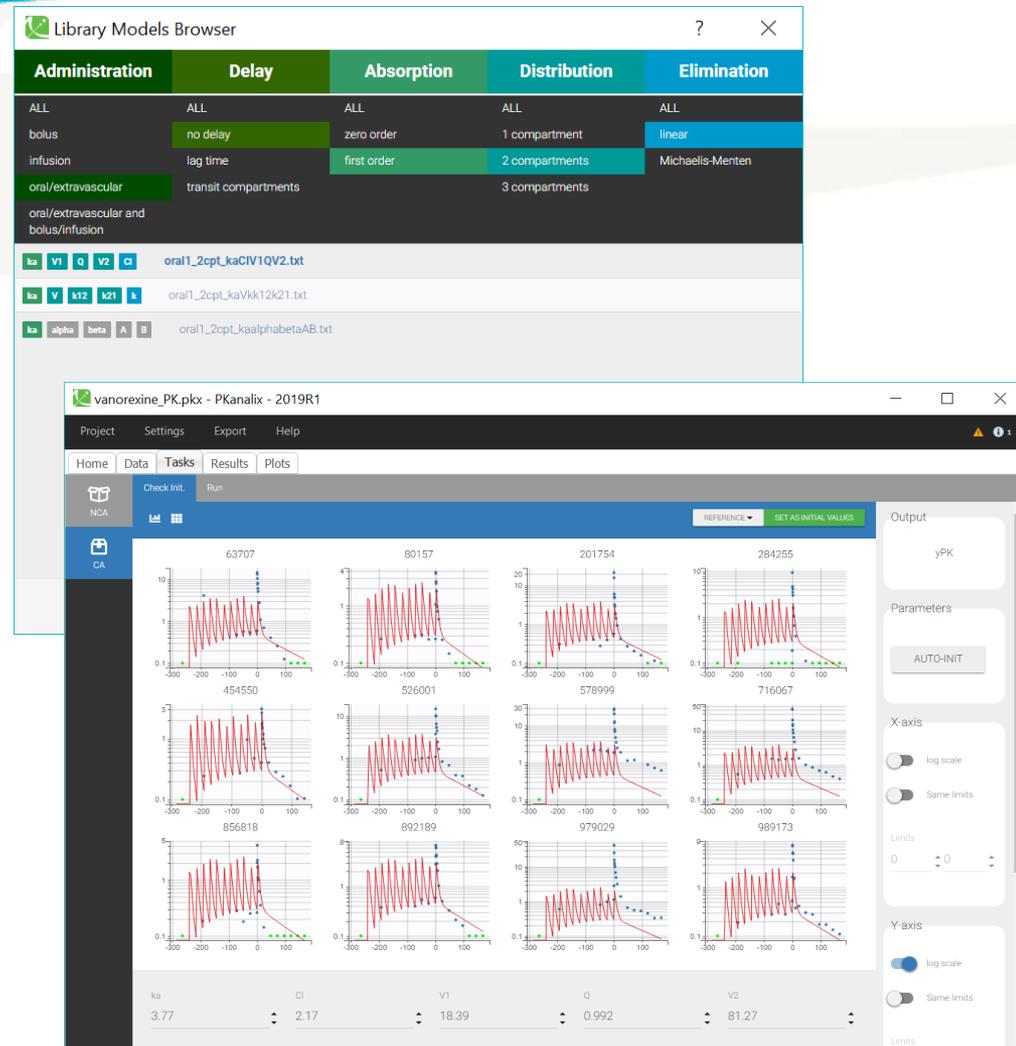
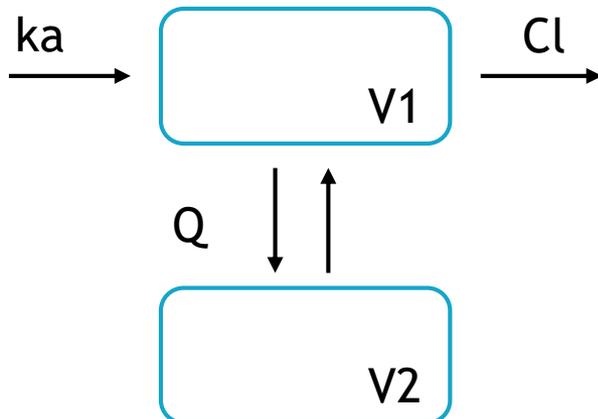
- Correlations of Dose with AUC, Cmax, and Cl, but not Tmax



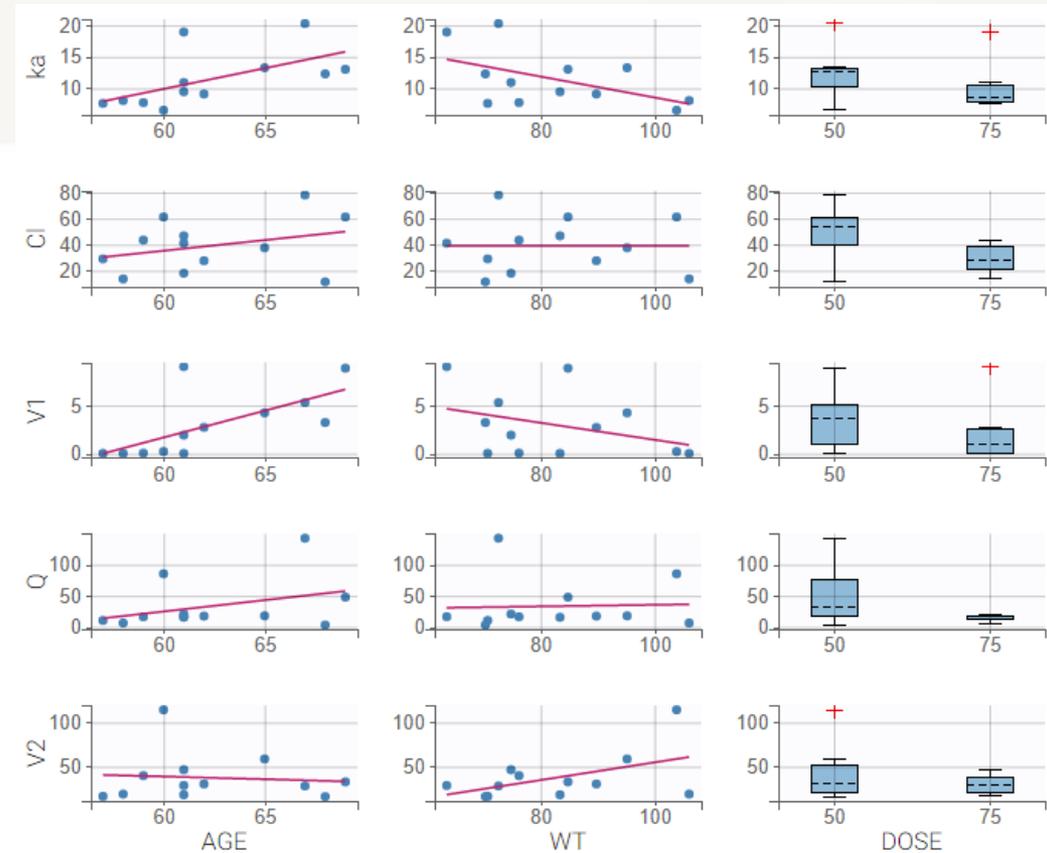
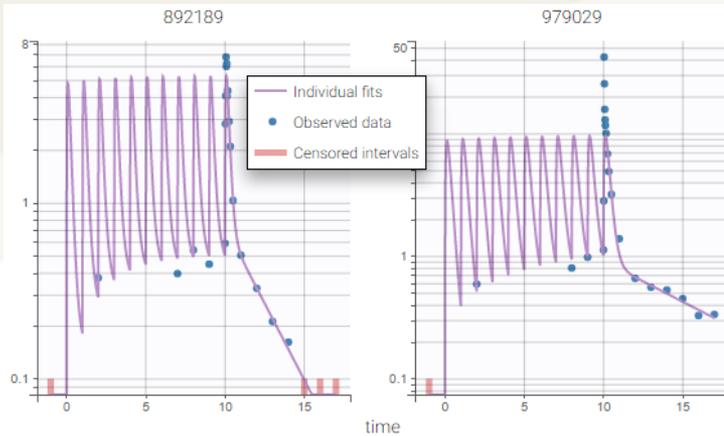
Fast CA:

- Model from PK library
- Automatic initialization

2-compartment model



CA with first-order kinetics and two compartments:



- At day 10, steady-state seems to be reached.
- All parameters except V_2 are correlated with the dose amount

➔ Assess the variability more precisely with population approach



1. Graphical exploration of the phase I data with Datxplore



2. Analyse the data with NCA and CA in Pkanalix



3. **Develop a popPK/PD model with Monolix**

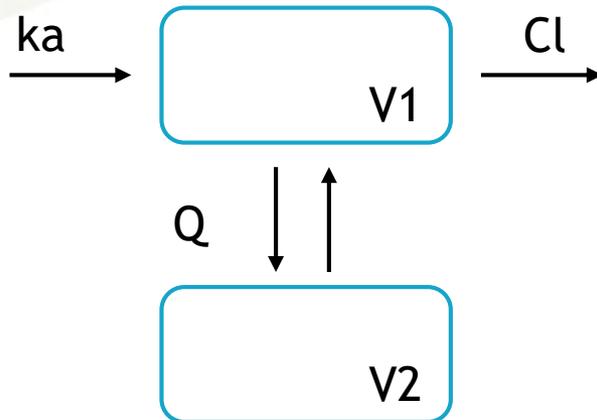


4. Simulate different situations to inform phase II trial design

Monolix: parameter estimation

- 2 compartments model from the PK library

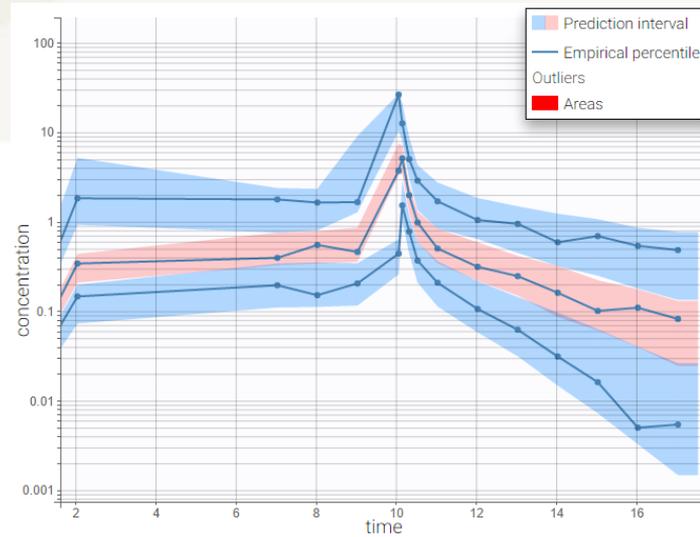
- No significant covariate effect
- Strong correlation between Cl, Q and V2



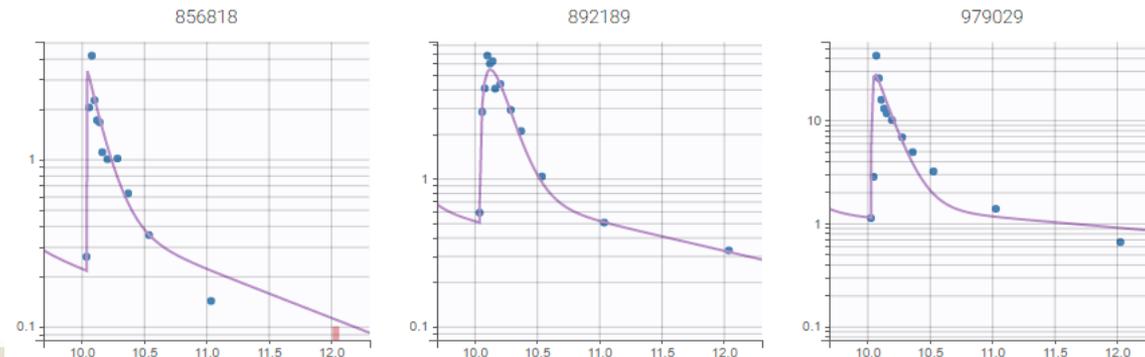
	VALUE	STOCH. APPROX.	
		S.E.	R.S.E.(%)
Fixed Effects			
ka_pop	8.15	0.391	4.8
Cl_pop	29.8	5.44	18.3
V1_pop	0.187	0.172	92.3
Q_pop	14.5	4.24	29.2
V2_pop	26	4.72	18.2
Standard Deviation of the Random Effects			
omega_Cl	0.628	0.128	20.4
omega_V1	1.75	0.632	36.1
omega_Q	0.984	0.207	21
omega_V2	0.597	0.128	21.4
Correlations			
corr_Q_Cl	0.803	0.102	12.8
corr_V2_Cl	0.675	0.173	25.6
corr_V2_Q	0.922	0.0585	6.34
Error Model Parameters			
b	0.262	0.0143	5.46

Monolix: parameter estimation

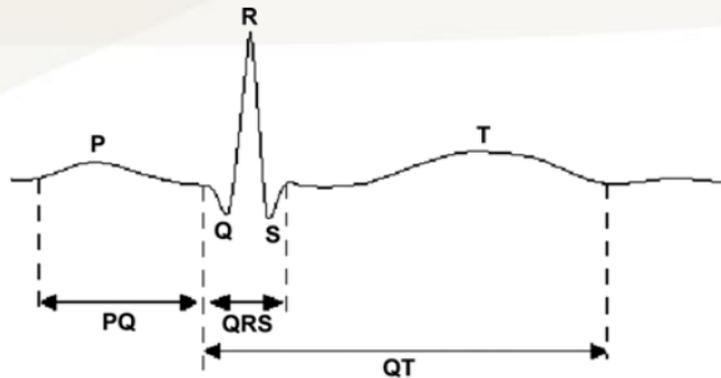
- Good predictive power of the model



- Good fit of absorptions for all individuals



QT interval prolongation carries a risk of sudden cardiac death.

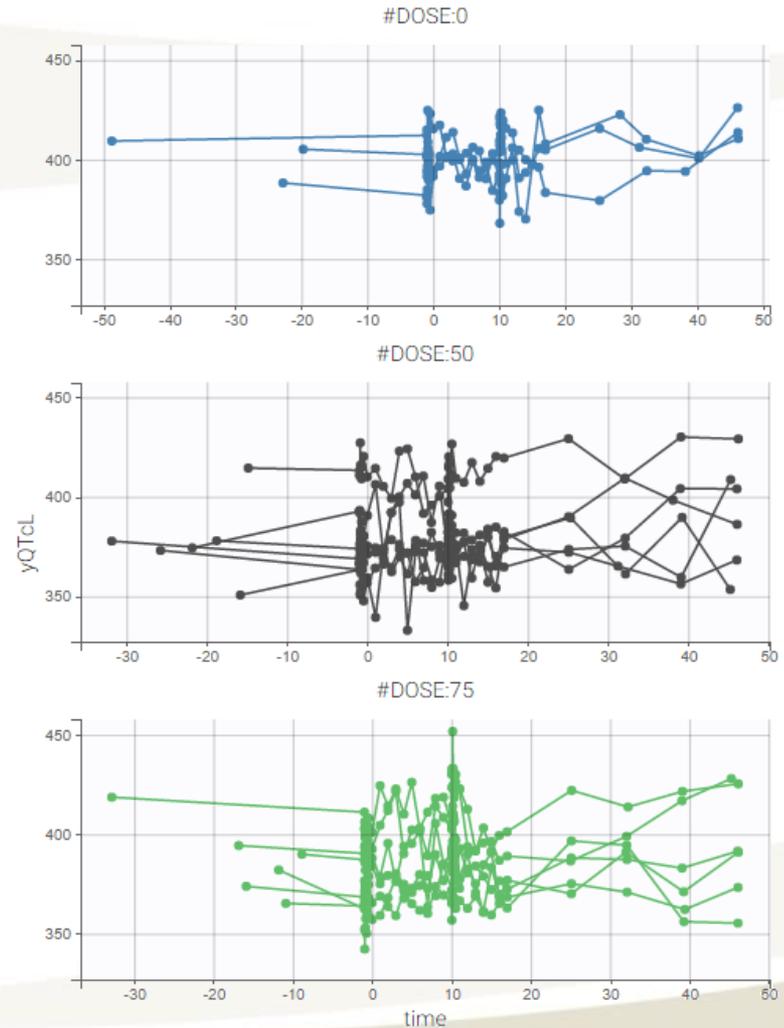


QT interval corrected for heart rate:

$$QTc = QT + 0.154 \times (1 - RR)$$

Sagie, A, Larson, MG, Goldberg, RJ, Bengtson, JR, Levy, D (1992). An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am. J. Cardiol.*, 70, 7:797-801.

15 patients with 3 placebo:



Population PD model for QTc interval

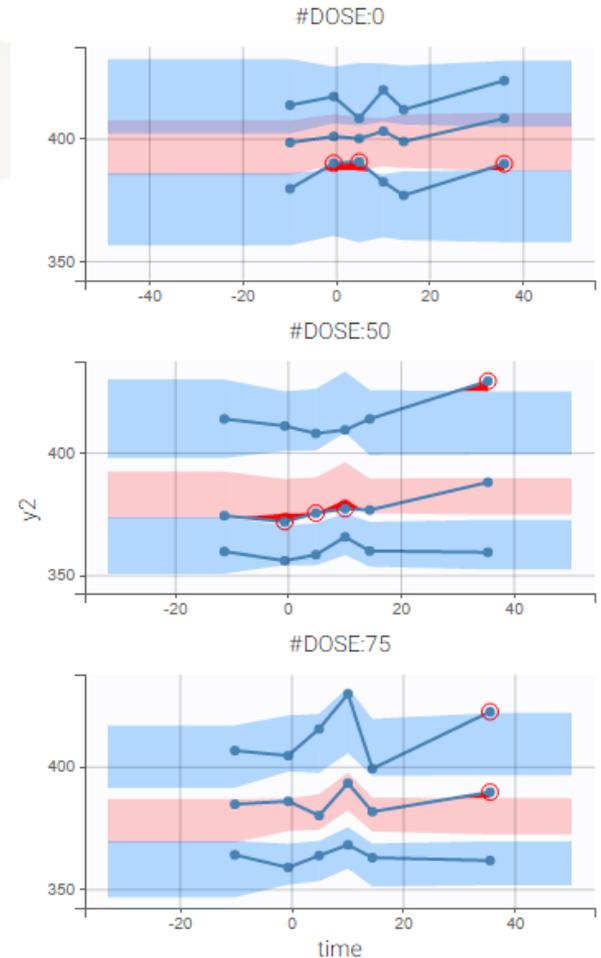


PD model from the library:
Emax model with sigmoidicity and effect compartment

$$E = E0 \times \left(1 + Emax * \frac{Ce^\gamma}{EC50^\gamma + Ce^\gamma} \right)$$

	VALUE	STOCH. APPROX.	
		S.E.	R.S.E.(%)
Fixed Effects			
ke0_pop	3.98	1.05	26.4
gamma_pop	3.88	1.66	42.8
E0_pop	344	12.9	3.75
beta_E0_GENDER_2	0.0873	0.0127	14.6
beta_E0_WT	0.00111	0.000442	39.7
Emax_pop	22	3.4	15.4
EC50_pop	2.72	0.387	14.2
Standard Deviation of the Random Effects			
omega_E0	0.0201	0.00377	18.8
Error Model Parameters			
a2	10.6	0.309	2.93

- Significant effect of GENDER and WT on E0
- High residual error due to high variability in data





1. Graphical exploration of the phase I data with Datxplore



2. Analyse the data with NCA and CA in Pkanalix



3. Develop a popPK/PD model with Monolix



4. **Simulate different situations to inform phase II trial design**

Based on the population model, can we predict the dose to reach concentration and safety targets?



1. Graphical exploration of the phase I data with Datxplore



2. Analyse the data with NCA and CA in Pkanalix



3. Develop a popPK/PD model with Monolix



4. **Simulate different situations to inform phase II trial design**

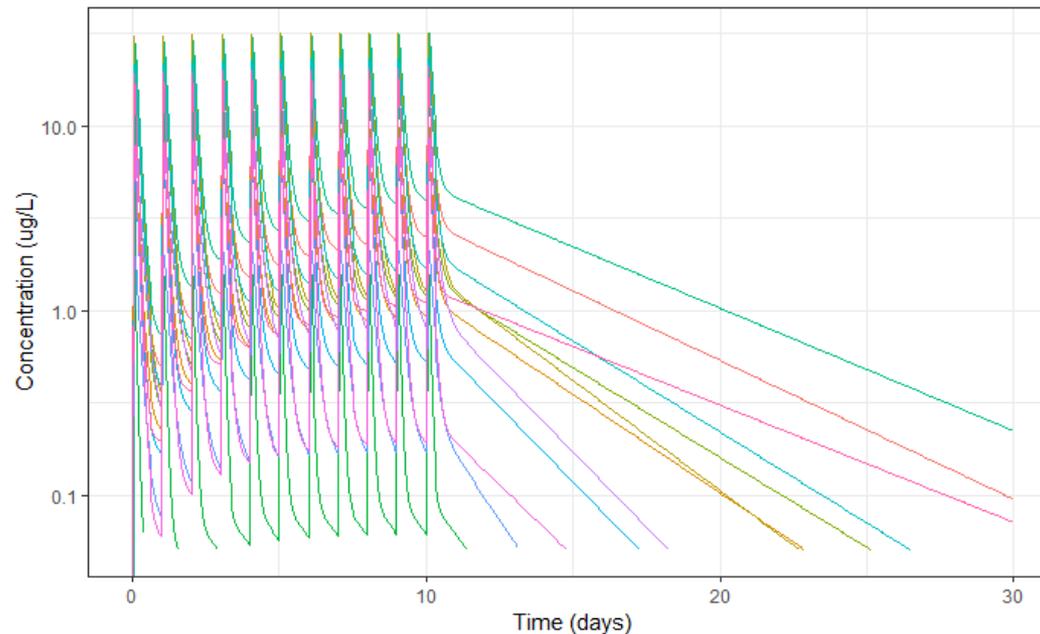
- ❑ Calculate different endpoints at therapeutic doses
- ❑ Assess efficacy and safety
- ❑ Compute the trial size
- ❑ Test different administrations

- **Check consistency with data**

Resimulate the project with regular measurement times and predictions with no error

```
outCc <- list(name='Cc', time=seq(0,40,by=0.1))
```

```
sim1 <- simulx(project = 'project_PK.mlxtran',  
              output = outCc)
```



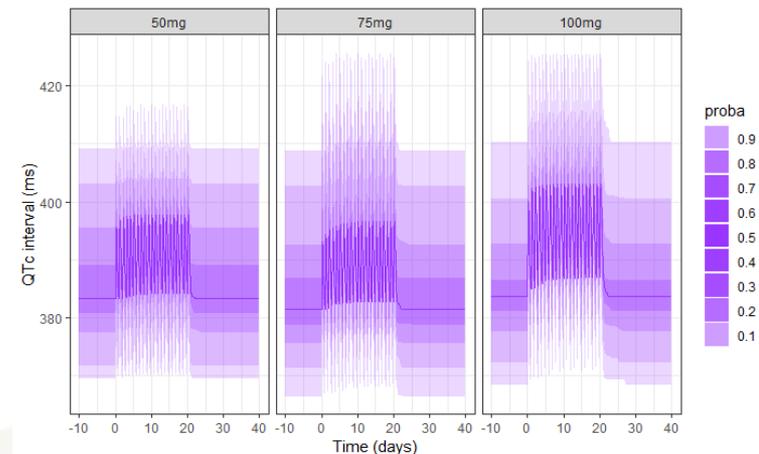
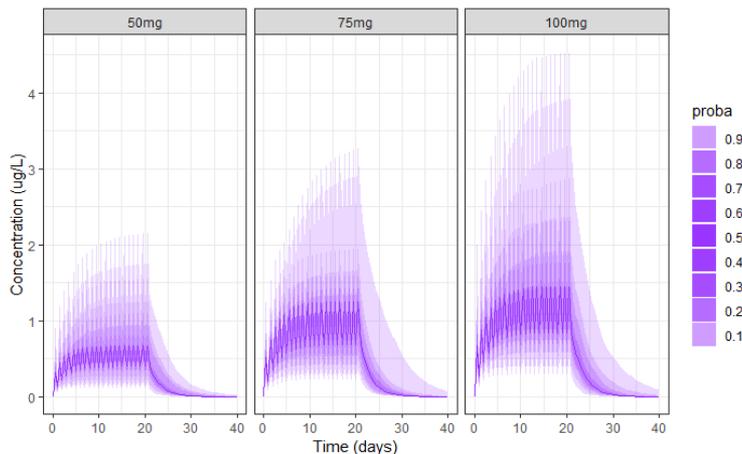
- **New dosing regimen:**

Simulate large populations (100 individuals) receiving 50mg/75mg/100mg during 20 days

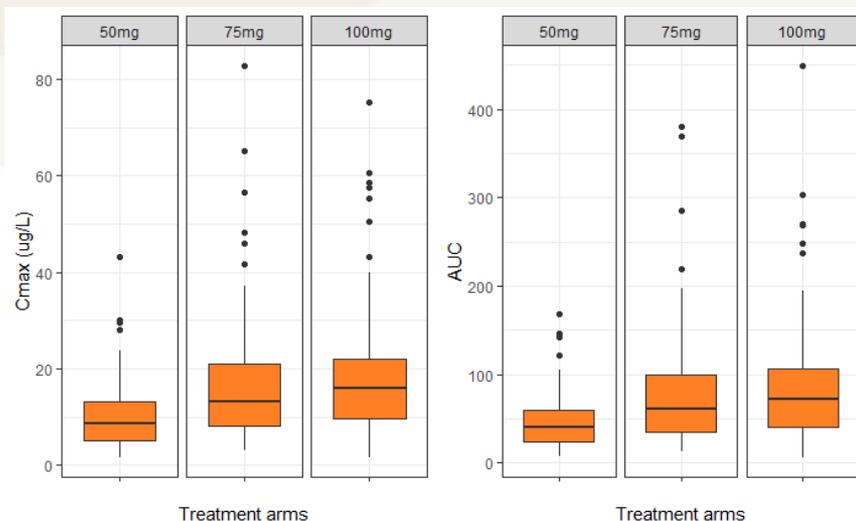
```
g50mg <- list(size=100, treatment = list(time=0:20, amount=50))  
g75mg <- list(size=100, treatment = list(time=0:20, amount=75))  
g100mg <- list(size=100, treatment = list(time=0:20, amount=100))
```

```
outCc <- list(name="Cc", time = seq(0, 40, by=0.01))  
outE <- list(name="E", time=seq(-10,40,by=0.1))  
outAUC <- list(name="AUC", time=40)
```

```
sim2 <- simulx(project = project_PKPD,  
              output = list(outCc, outE, outAUC),  
              group = list(g50mg, g75mg, g100mg),  
              addlines = list(formula=c("ddt_AUC = Cc")))
```

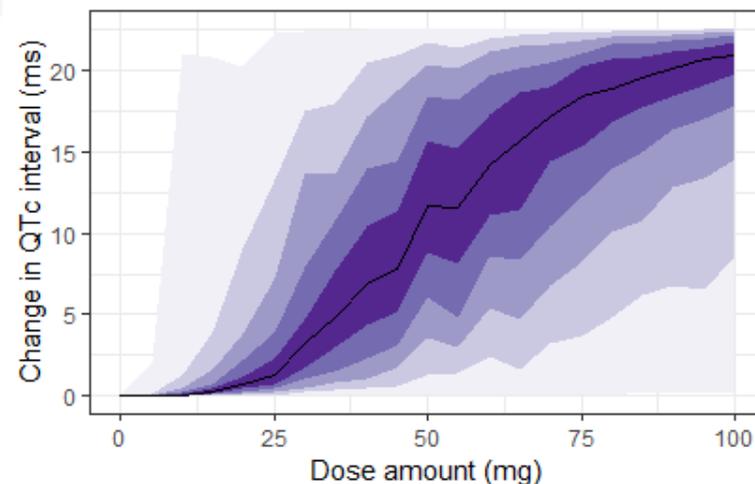


- Assess results of new dosing regimen:
Compute several endpoints and assess variability in the population



Dose	Patients with Cmax > 2ug/L	Patients with Cmax > 4ug/L
50mg	98%	83%
75mg	98%	95%
100mg	100%	97%

Simulation-based curves for QTc interval prolongation vs. the dose amount.



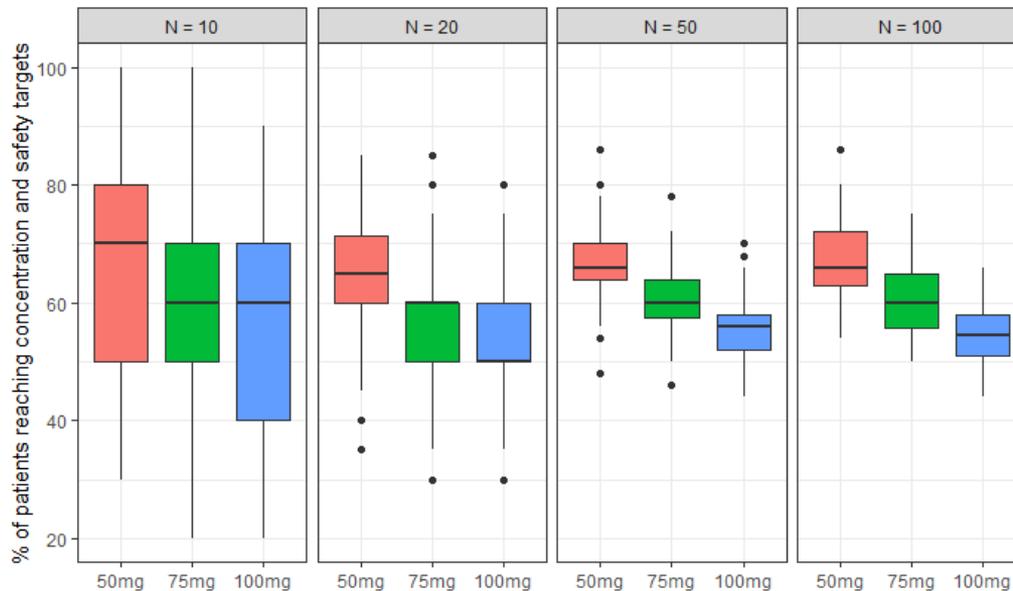
Dose	Patients with change of QTc interval from baseline > 20ms
50mg	20%
75mg	44%
100mg	51%

- Assessing the success of clinical trials with different population sizes

Simulate clinical trial with 3 treatment arms and 10, 20, 50 or 100 individuals per group, and 100 replicates for each simulation.

Endpoint: percentages of patients achieving

- a maximal change of QTc from baseline of 20ms.
- a minimum Cmax of 2ug/L.



Probability of success compared to reference treatment (50mg)

Nindiv	75mg	100mg
10	0.00	0.02
20	0.00	0.06
50	0.04	0.35
100	0.27	0.82

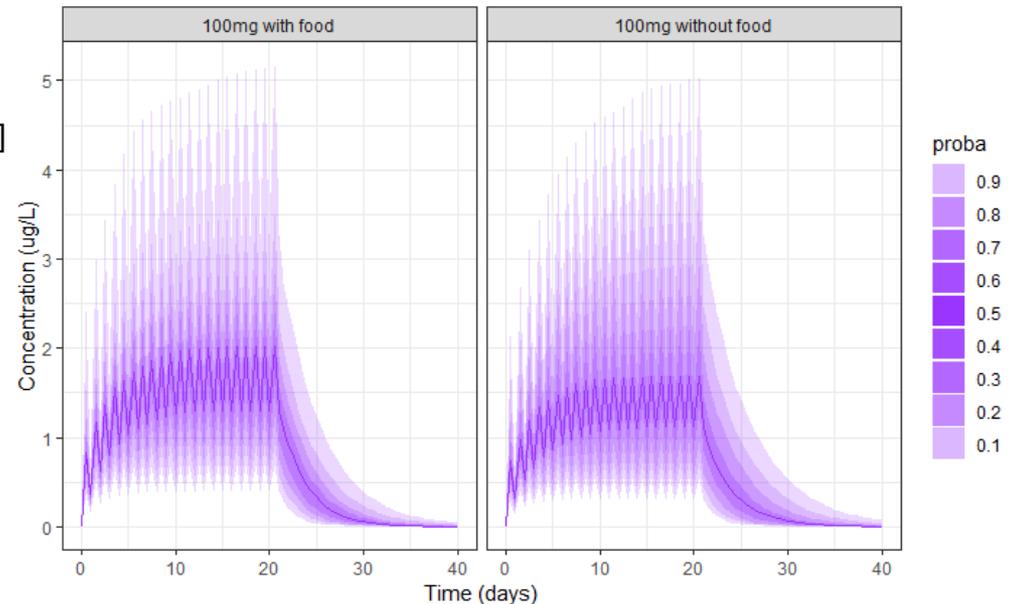
Simulations of clinical trials with replicate allow to predict the uncertainty of the results

- **New parameters:**

Assess the effect of food causing increased bio-availability (Ingwersen *et al.*, 1993b), implemented as smaller V_{pop} in the model.

```
params <- sim1$population["V1_pop", "Cl_pop"]  
params_withFood <- params/1.2  
trt <- list(time=0:20, amount=100)
```

```
sim_food <- simulx(project = project_PK,  
  output = outCc,  
  treatment = trt,  
  group = list(size=200),  
  parameter = params_withFood)
```



The model or parameters can be modified to test new situations

- Data from phase I studies can be easily analyzed and modeled with the MonolixSuite.
- In-silico simulations of various situations can be used to inform clinical trial design.

- **Vanorexine example:**
 - Fast modelling workflow with models from the library.
 - Parameters are estimated despite high variability in PD data.
 - This model can be used to guide the choice of subsequent clinical trials, taking into account both efficacy and safety.

Conclusion

Meet us at the Lixoft booth!



www.lixoft.com