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# Population pharmacokinetic model of cefotaxime encompassing time-varying physiopathology: exploration of intra-individual variability of the renal function

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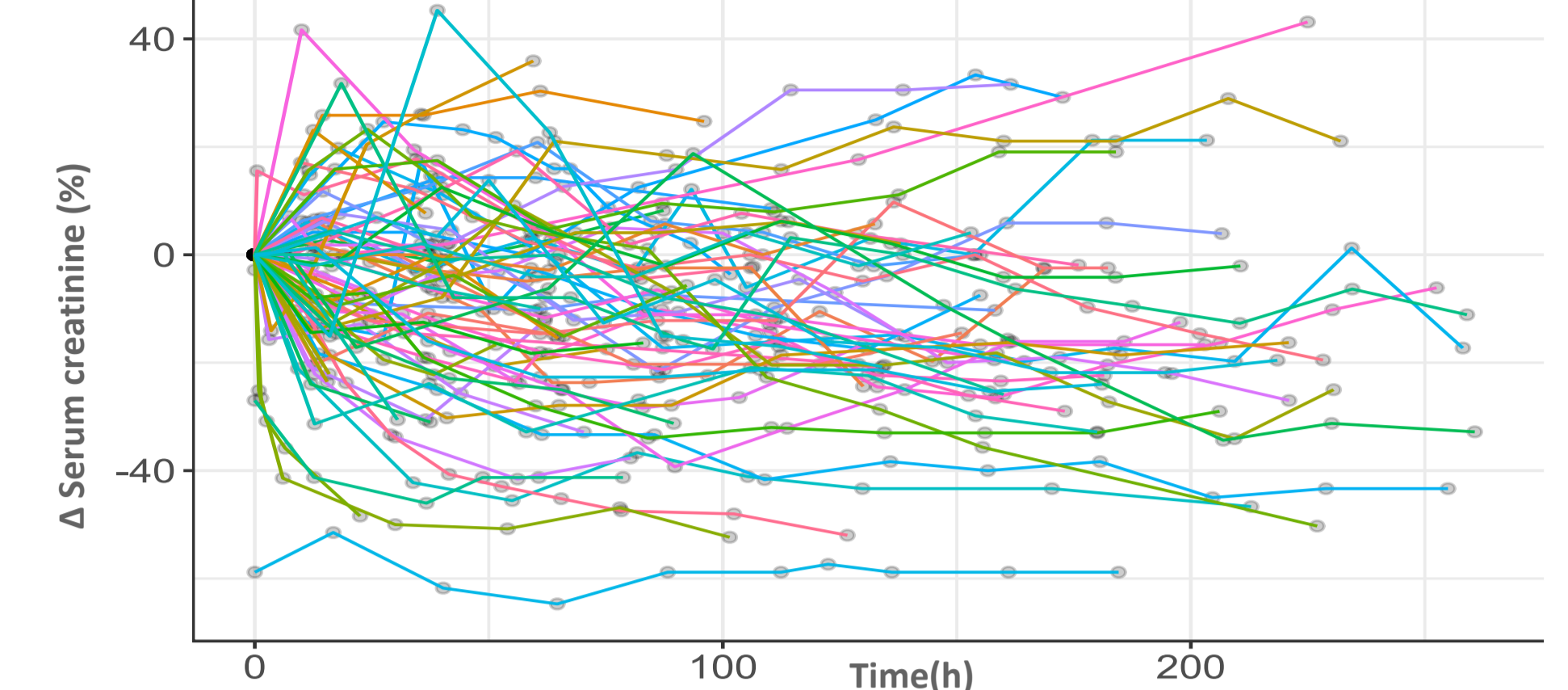
## BACKGROUND

Critically ill patients → Patho-physiological modifications

→ High inter- and intra-individual pharmacokinetic (PK) variability

→ Supra- or sub-therapeutic concentrations<sup>[1]</sup>

→ Need for a personalized drug dosing regimen



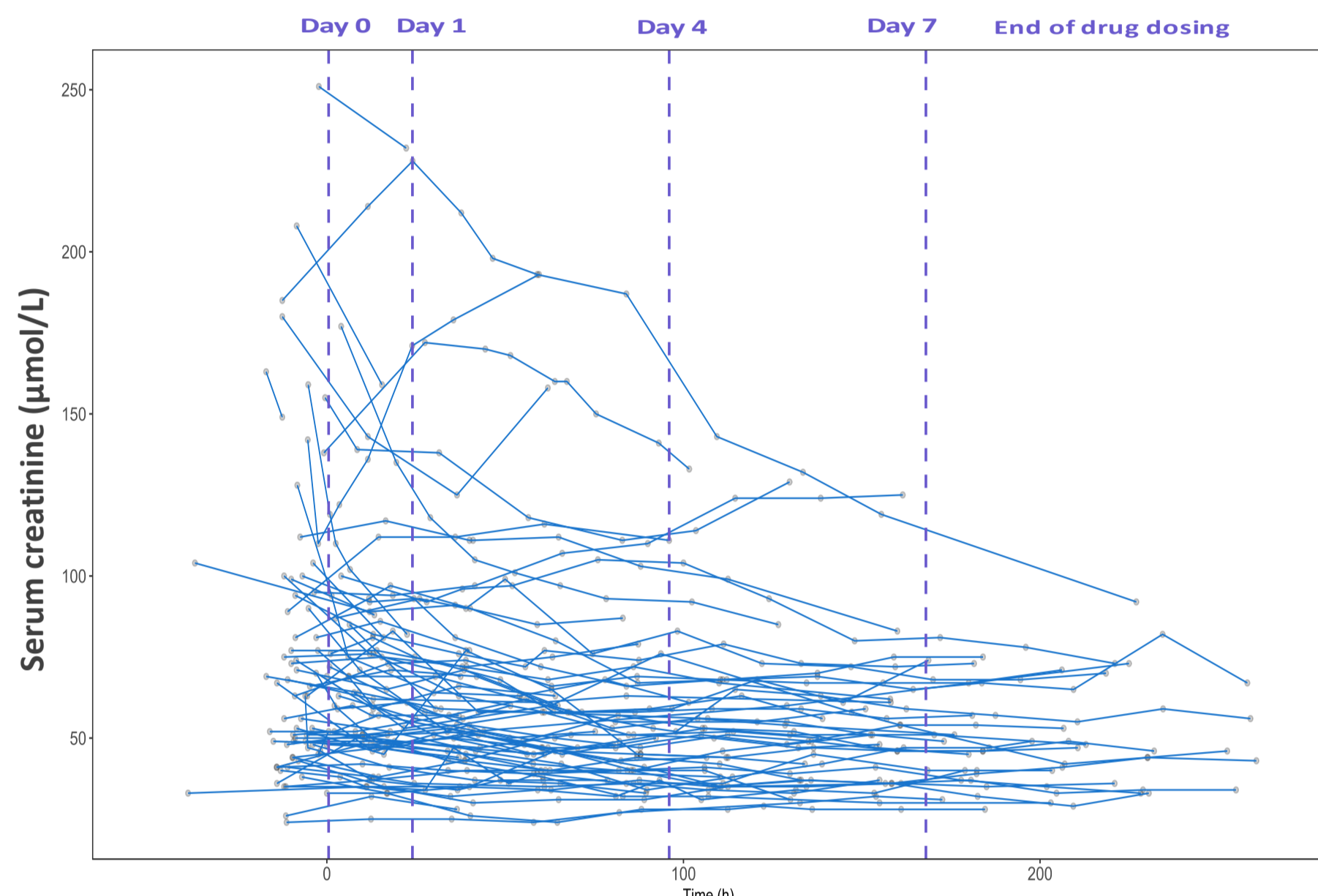
**Serum creatinine evolution**  $\Delta \text{Serum creatinine} = \left( \frac{\text{Serum creatinine} - \text{Serum creatinine}_{\text{Baseline}}}{\text{Serum creatinine}_{\text{Baseline}}} \right) \times 100$   
Grey dots: observed data. Lines: One color per individual

**Aim:** To perform a priori dosing adjustment of cefotaxime based on a biomarker model of renal function

## METHODS

### STUDY DESIGN

- Prospective, multicenter, observational study (Oct. 2015 - May 2017) in Intensive Care Units (ICU) of Marseille.
- Cefotaxime dosing regimen: loading dose (2g-4g/0.5h) followed by continuous infusion (1-24g/24h) over 7 days



Constant covariates: median [Range] or number

Age (years)	57 [19-86]
Male/Female	45/31
Height (cm)	170 [150-190]
Weight (kg)	73 [48-125]
Body surface area (BSA, m <sup>2</sup> )	1.87 [1.44-2.60]
Body mass index (BMI, kg/m <sup>2</sup> )	25.25 [16.61-44.08]
SAPS_II score	39 [12-105]

Time-varying covariates

Hematocrit
Indexed clearance (iCLcr)
SOFA score
Serum albumin
Serum Creatinine
Serum urea
Estimated clearance (eCLcr)

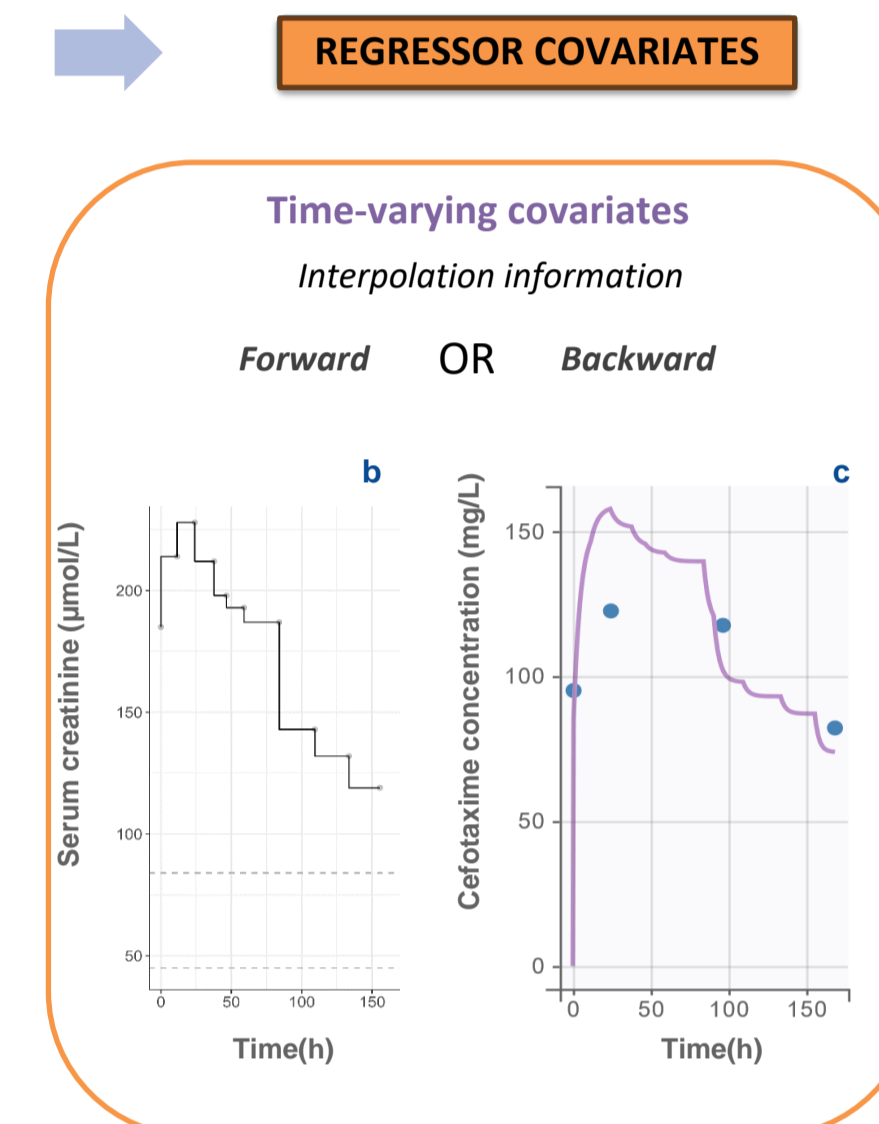
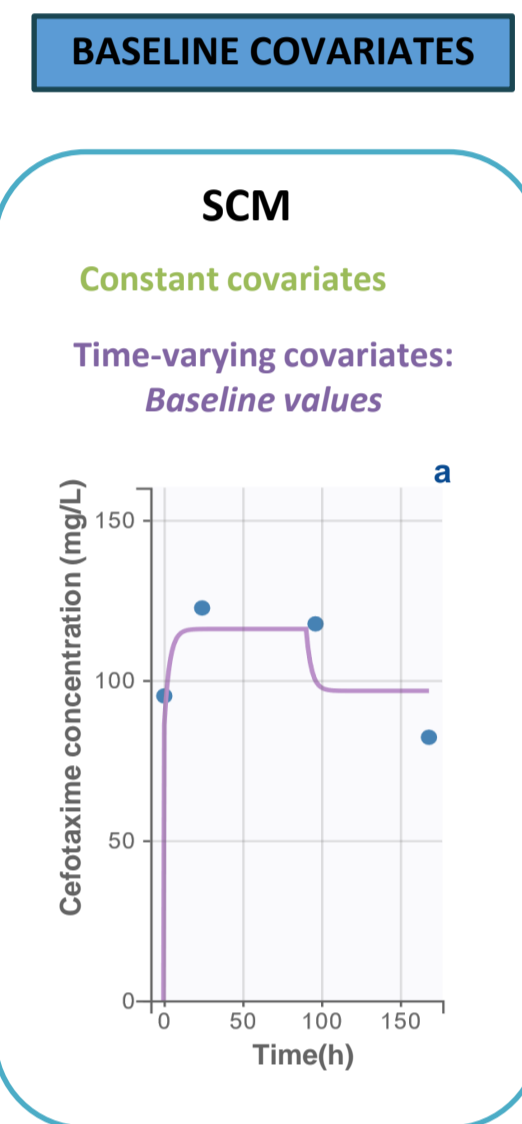
**Covariates:** Constant covariates collected at inclusion; Time-varying covariates collected every 24h

BSA: body surface area determined using the Dubois and Dubois formula, Severity score: SAPS\_II Simplified Acute Physiology Score 2, SOFA: Sepsis-related Organ Failure Assessment, estimated creatinine clearance determined using the Cockcroft and Gault formula, indexed clearance creatinine:  $iCLcr = \frac{1.73}{BSA} \times \left( \frac{\text{Urine creatinine} \times \text{Urine volume}}{\text{Serum creatinine}} \right)$

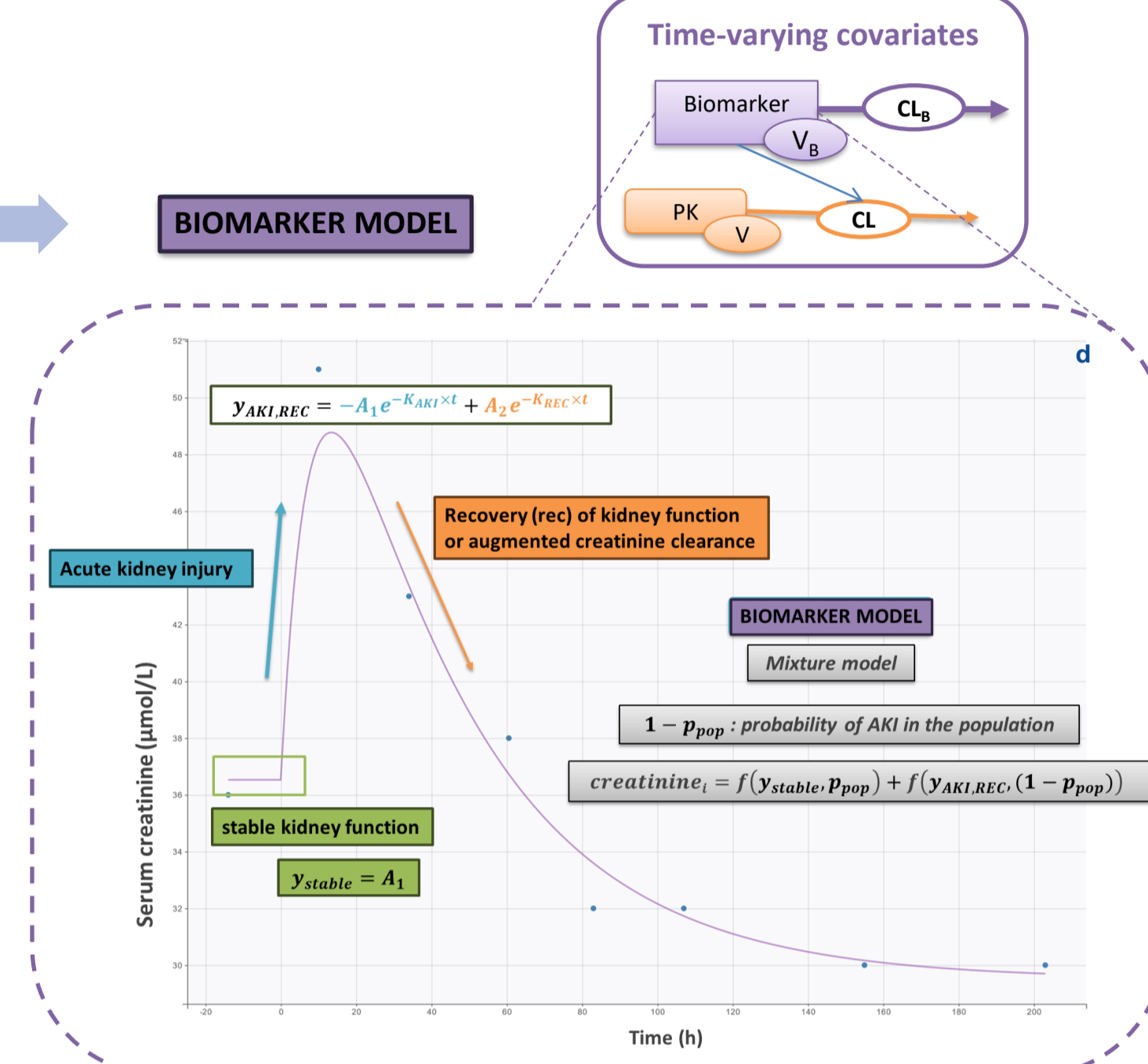
### POPULATION PK ANALYSIS PLAN

251 cefotaxime concentrations

BASE MODEL: Structural model (without covariates)  
Data below the limit of quantification: left-censored



523 serum creatinine concentrations



**Analysis:** MONOLIX® 2023R1 software. a) Cefotaxime concentrations: representative individual fit with baseline serum creatinine. b) Serum creatinine: representative individual fit with backward interpolation. c) Cefotaxime concentrations: representative individual fit with backward interpolation. d) Serum creatinine: representative individual fit with a biomarker model

SCM: stepwise covariate model procedure with forward ( $\alpha=0.05$ ) and backward steps ( $\alpha=0.01$ ), power and exponential covariate relationships tested  
Purple line: individual prediction, blue dot: observed data, black line: backward interpolation, blue dot: observed data, dashed grey line: normal values

## RESULTS

### POPULATION PK MODEL OF CREATININE

Parameter	Base model		Final model	
	Estimates	RSE (%) [SHR](%)	Estimates	RSE (%) [SHR](%)
<b>Fixed effects</b>				
A <sub>1</sub> (µmol/L)	72.7	6.09	75.67	4.88
A <sub>2</sub> (µmol/L)	114	10.8	105	7.28
K <sub>AKI</sub> (1/h)	0.021	30.7	0.025	22.1
K <sub>REC</sub> (1/h)	0.022	18.7	0.023	13.9
P <sub>pop</sub>	0.77	2.08	0.73	2.47
<b>Covariate effects</b>				
βA <sub>1_urea</sub>			0.39	24.1
βA <sub>2_urea</sub>			0.91	14.8
<b>Random effects</b>				
IIV A <sub>1</sub>	0.41	11.4 [-9.01]	0.35	11.4 [-6.4]
IIV A <sub>2</sub>	0.81	10.4 [3.24]	0.51	10.4 [0.406]
IIV K <sub>AKI</sub>	1.47	19.3 [11.7]	1.1	19.3 [13.6]
IIV K <sub>REC</sub>	0.99	18.2 [7.37]	0.84	18.2 [-7]
IV P <sub>pop</sub>	0.26	16.1 [3.59]	0.28	16.1 [-5]
ε	0.075	4.23	0.075	4.49

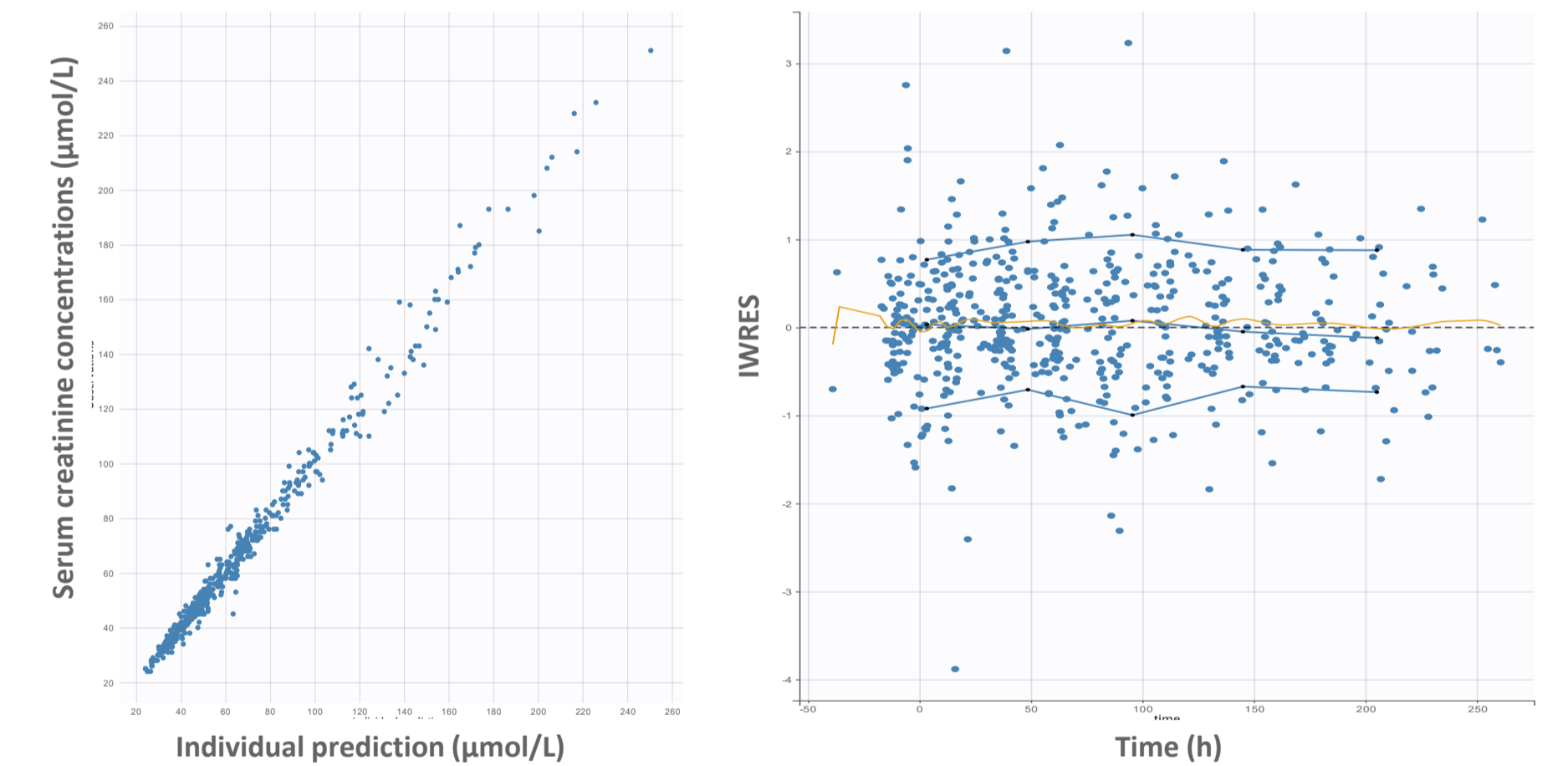
#### Parameter estimates

RSE relative standard error  
SHR shrinkage  
AKI: Acute kidney injury  
REC: recovery of kidney function  
Green: baseline covariates  
IIV inter-individual variability,  
ε proportional residual error

#### Goodness of fit plots

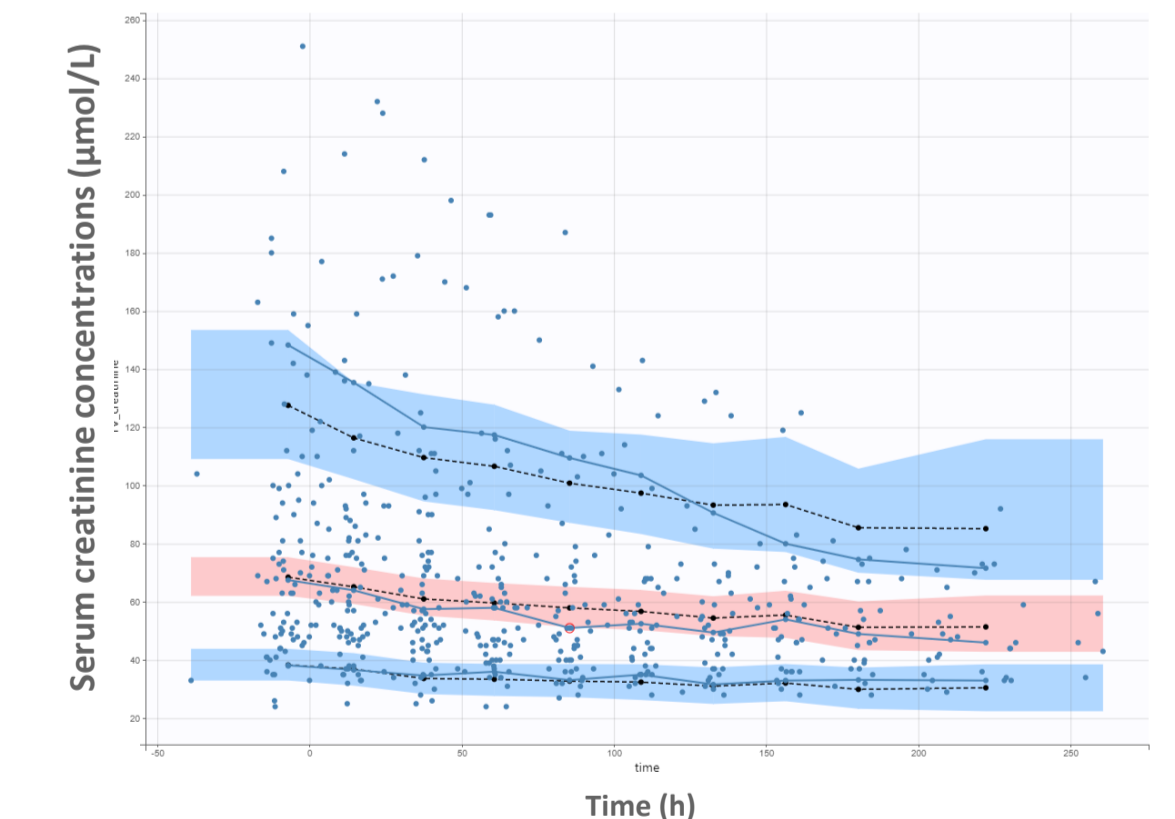
Orange line: spline, dashed black line: 90% prediction interval, IWRES: individual weighted residuals, dashed line: theoretical mean, blue line: empirical percentiles

### MODEL EVALUATION



#### Visual Predictive Check

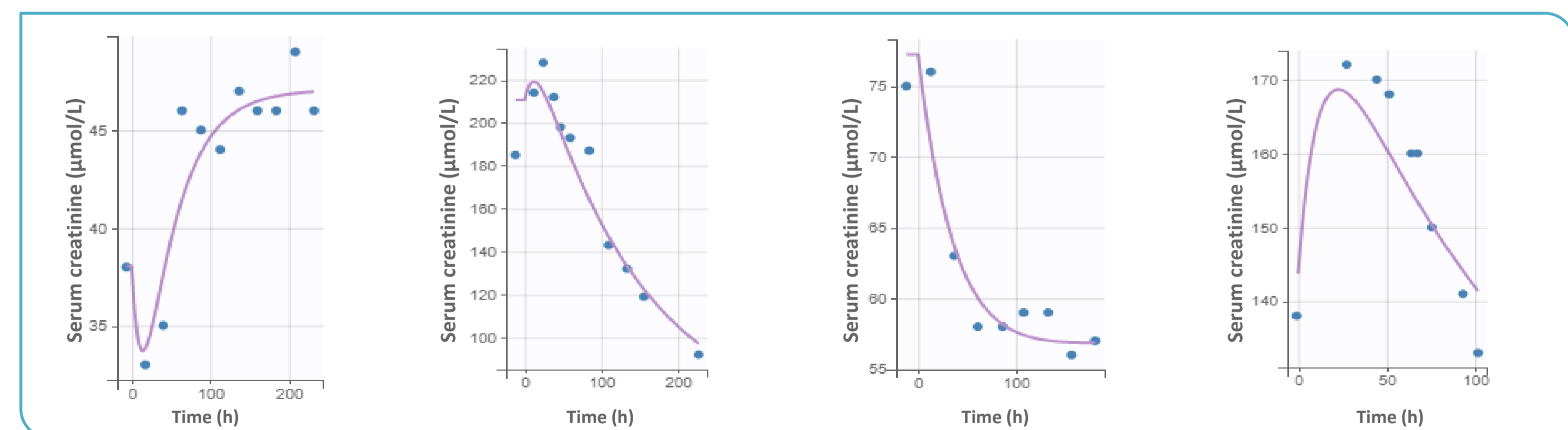
blue solid lines: 5<sup>th</sup>, 50<sup>th</sup> and 95<sup>th</sup> percentiles of observed data, shaded areas: 95% confidence interval of the simulated 50<sup>th</sup> (red), 5<sup>th</sup> and 95<sup>th</sup> (blue) percentiles respectively



→ Intra-individual variation of probability of constant or first order model

- Detection of changes between normal renal function and AKI
- Detection of changes between AKI and recovery of renal function

→ Serum urea concentration explains part of the IIV of creatinine levels



**Representative individuals for creatinine with biomarker model**  
a,b,c,d: purple line: individual prediction of serum creatinine model, blue dot: observed data

→ Good fit, no bias

→ Prediction of next creatinine concentrations

## CONCLUSION

- High inter- and intra-variability of renal function in ICU patients was partly explained by time-varying creatinine covariate
- A predictive model of serum creatinine evolution has been developed
- We will combine a cefotaxime Pop-PK model with the creatinine biomarker model

#### Contact

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