An optimised fluconazole dosing strategy in critically ill patients

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IATDMCT, Singapore
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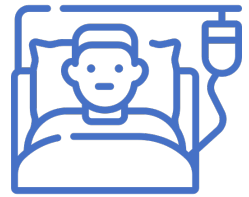
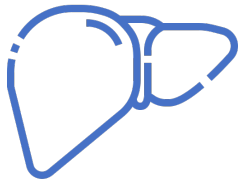
Fluconazole overview

- Antifungal drug 
- Stepdown treatment of invasive candidiasis in critically ill patients[1] 
- Excreted via kidneys[2] 
- Minimal hepatic metabolism[2] 

[1]Pappas PG et al. Clin Infect Dis (2016) 4, e1-50.

[2]Pfizer. Summary of Product Characteristics (SmPC) Diflucan (2012).

Fluconazole PKPD

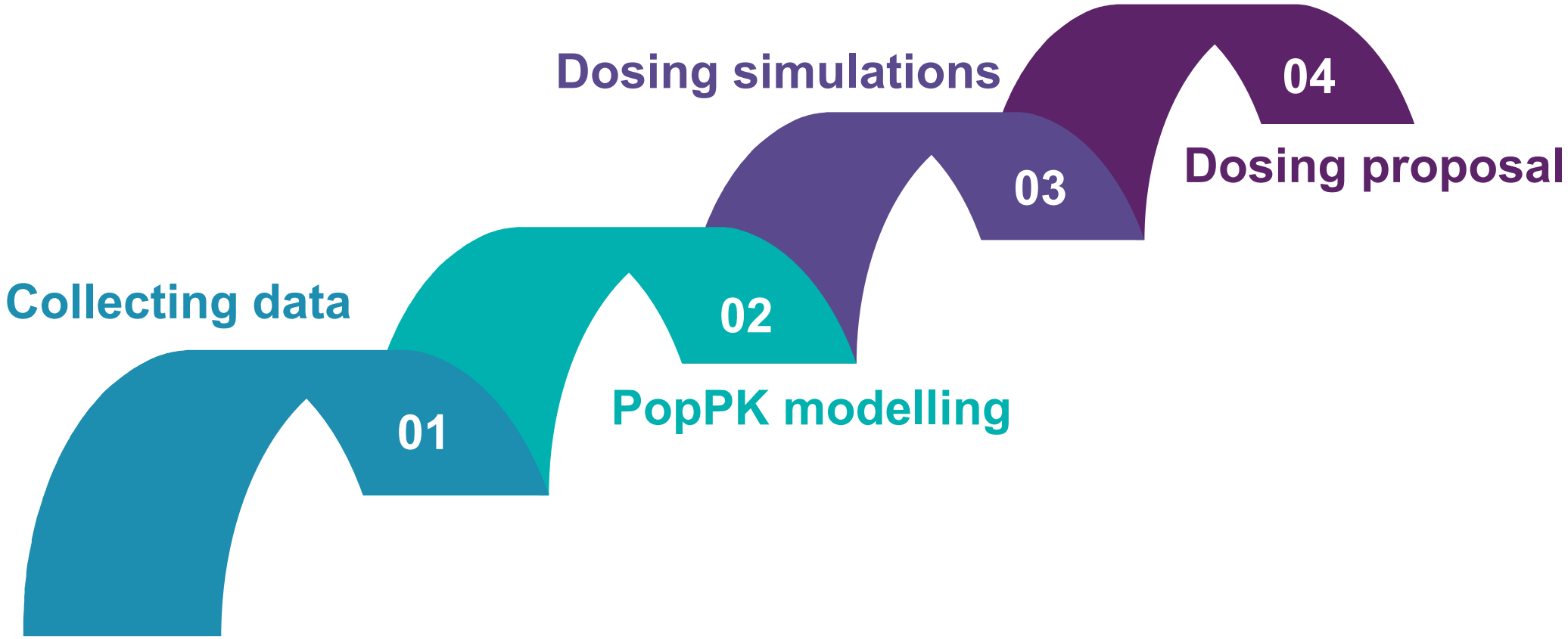
- $fAUC_{0\text{-}24}$/MIC ≥100[1]

- PKPD target is not always reached

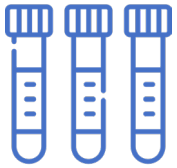
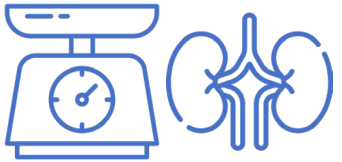
1. Identify clinically relevant covariates
2. Provide an optimised dosing recommendation

[1]European Committee on Antimicrobial Susceptibility Testing. Fluconazole: Rationale for the clinical breakpoints, version 3.0 2020.

A 4-step workflow



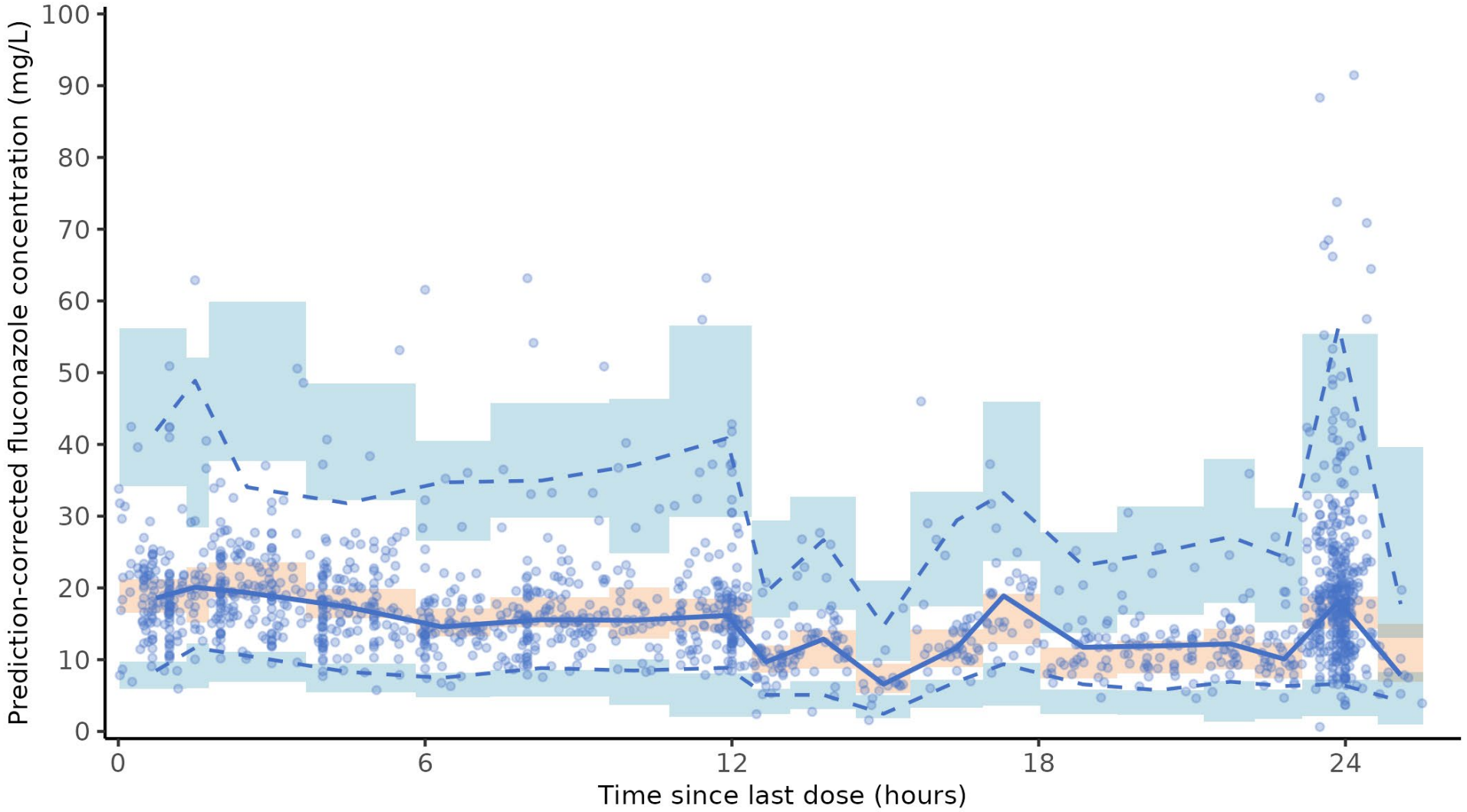
An individual patient data meta-analysis

- 8 studies, 7 clinical centres, 177 ICU patients 
- 1616 concentrations – median [IQR]: 7 [3-12] concentrations/patient 
- Body weight: 34-142 kg, $eGFR_{CKD\text{-}EPI}$: 7-213 ml/min/1.73m^2 
- 19.2% CRRT at least once 
- Missing covariates: body weight: 2.8%, $eGFR_{CKD\text{-}EPI}$: 59.3% 

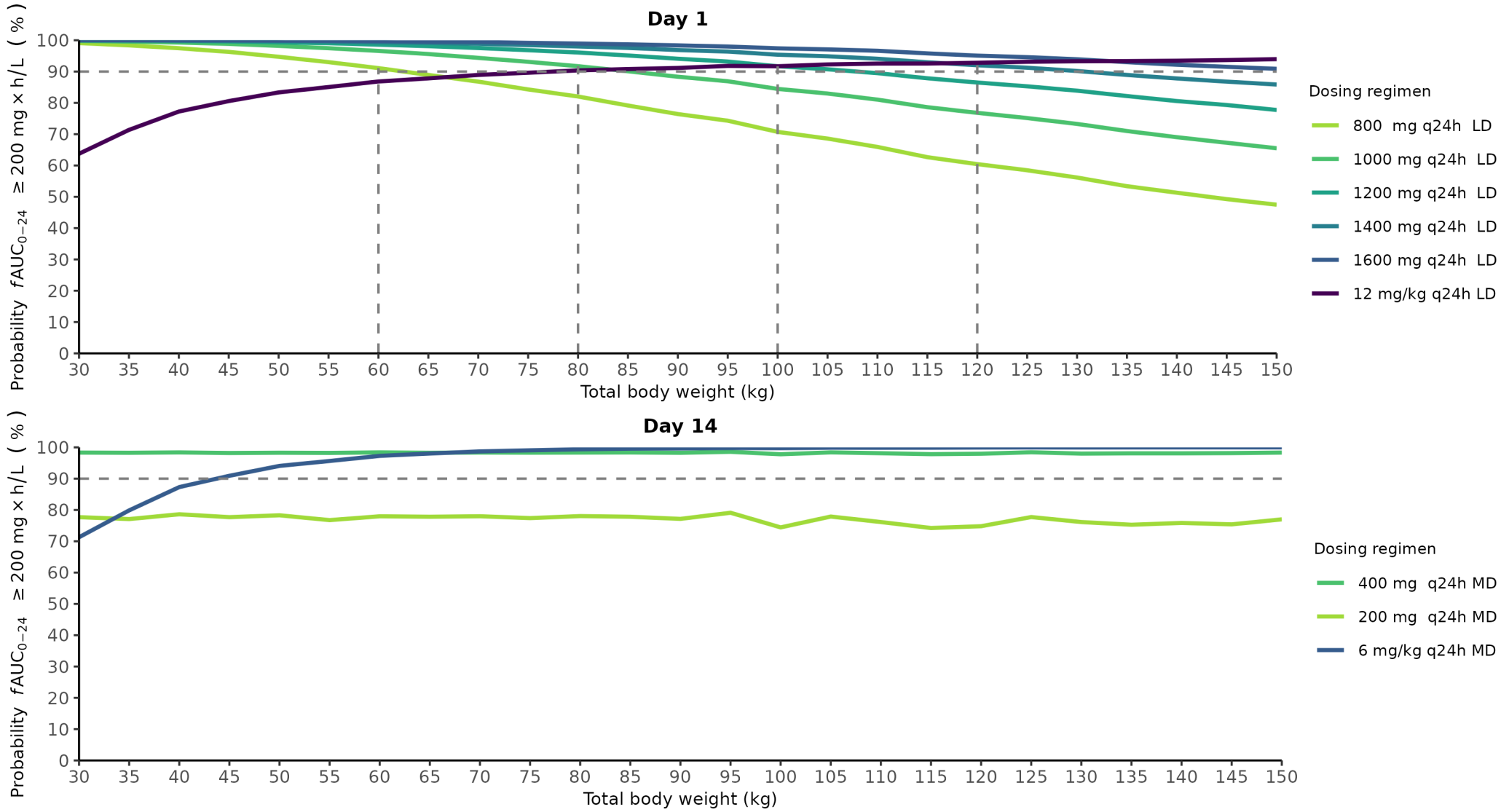
PopPK model estimates

Structural parameters	Final model estimate (95% CI)
$Cl_{on\text{-}CRRT}$ **(L/h)**	1.56 (1.25–1.87)
$CL_{off\text{-}CRRT}$ **(L/h)**	0.614 (0.548–0.679)
$eGFR_{CKD\text{-}EPI}$ on $CL_{off\text{-}CRRT}$	0.532 (0.131–0.933)
Vc (L)	39.4 (33.1–45.7)
Body weight on Vc	0.908 (0.498–1.317)
Q (L/h)	12.1 (3.7–20.5)
V_p (L)	8.47 (2.73–14.20)

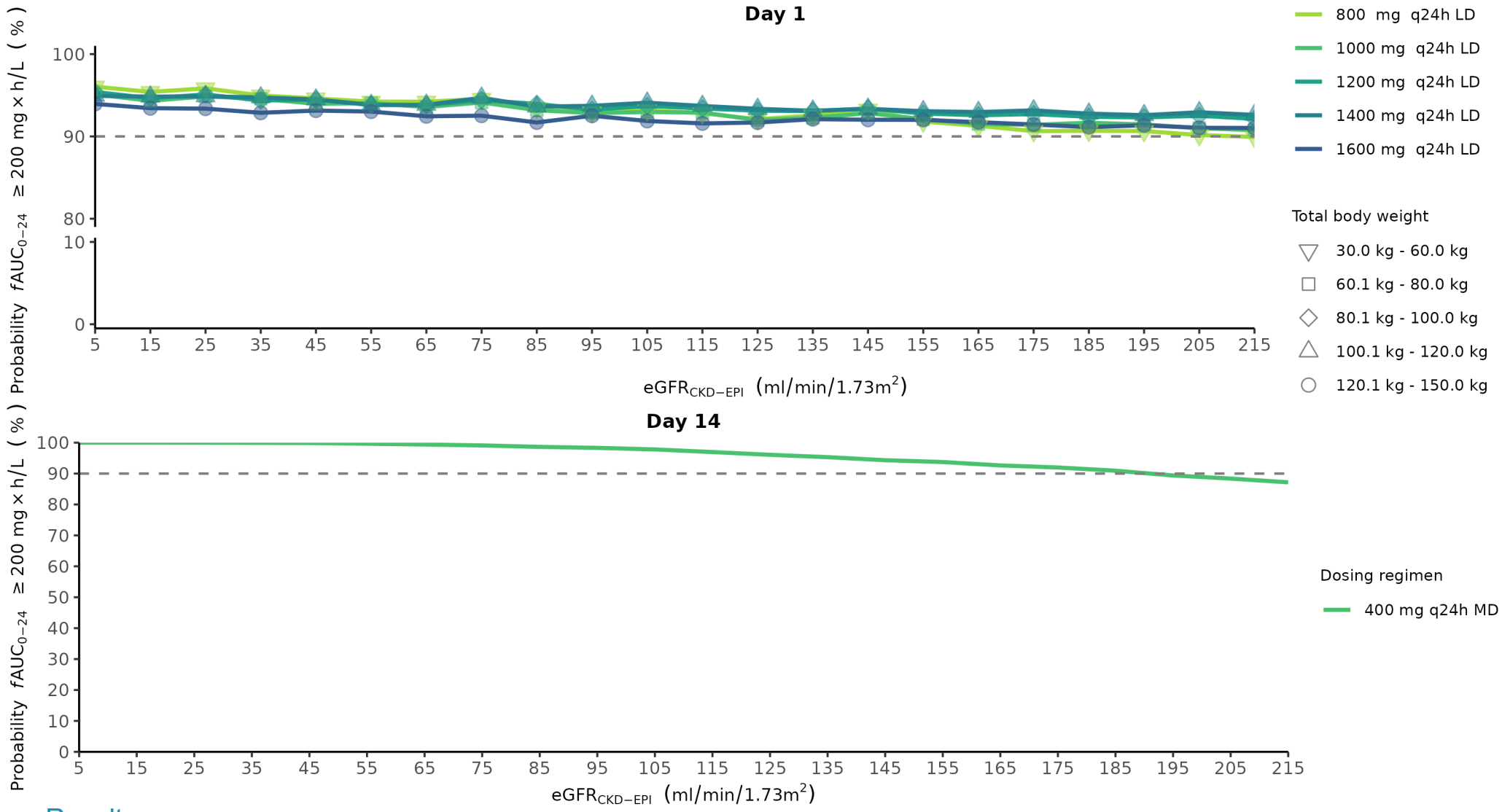
The model is well calibrated



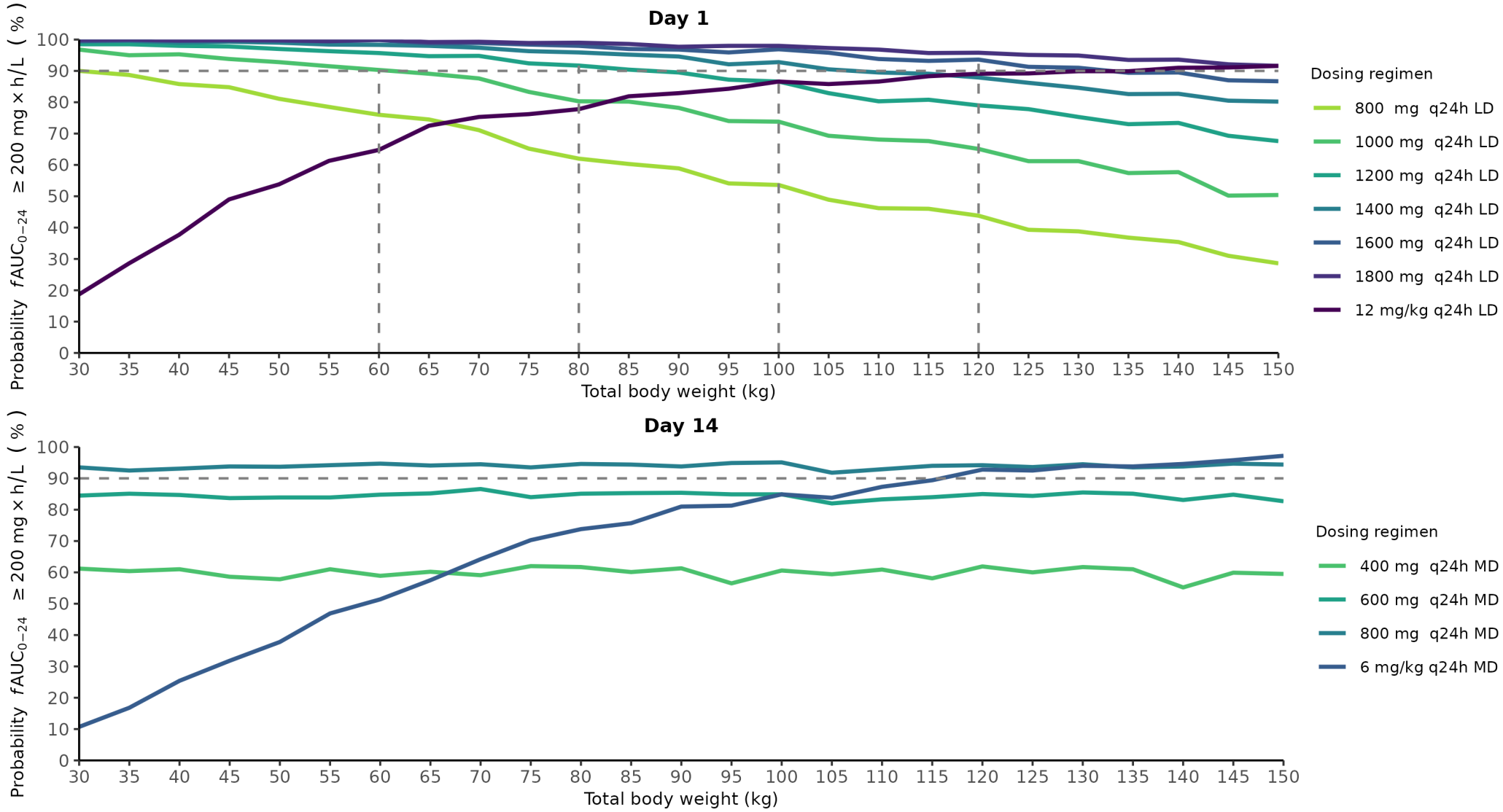
Impact of body weight when off-CRRT



Impact of kidney function when off-CRRT



Impact of body weight when on-CRRT



Optimised dosing regimen proposal

Body weight	Off-CRRT		On-CRRT	
	Loading dose (day 1)	Maintenance dose (from day 2)	Loading dose (day 1)	Maintenance dose (from day 2)
30.0 kg - 60.0 kg	800 mg q24h	400 mg q24h	1000 mg q24h	800 mg q24h
60.1 kg - 80.0 kg	1000 mg q24h		1200 mg q24h	
80.1 kg - 100.0 kg	1200 mg q24h		1400 mg q24h	
100.1 kg - 120.0 kg	1400 mg q24h		1600 mg q24h	
120.1 kg - 150.0 kg	1600 mg q24h		1800 mg q24h	

Conclusions

- Body weight and CRRT status are the two clinically relevant covariates
- We provided an optimized dosing regimen >> await prospective validation

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