

From capillary to clinic: Model-based translation of volumetric absorptive microsampling concentrations for therapeutic drug monitoring of CABO

Chrisoula Tahtsidou^{1, 2}, Fenja Klima^{2, 3}, Jonas Huhn¹, Nouredin Sharaf¹, Nora Isberner⁴, Juliane Staudinger⁵, Georg Hempel⁵, Ulrich Jaehde⁶, Charlotte Kloft^{2, 3}, Oliver Scherf-Clavel¹

(1) Clinical Pharmacy and Pharmacotherapy, Department of Pharmacy, Ludwig-Maximilians-Universität München, Munich, Germany. (2) Graduate Research Training Program PharMetX, Berlin/Potsdam, Germany. (3) Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universität Berlin, Berlin, Germany. (4) Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany. (5) Department of Clinical Pharmacy, Institute of Pharmaceutical and Medical Chemistry, University of Münster, Germany. (6) Department of Clinical Pharmacy, Institute of Pharmaceutical Sciences, University of Bonn, Bonn, Germany.

Background

-  Cabozantinib (CABO): used in advanced **renal cell carcinoma**.
-  TDM supports identification of **suboptimal concentrations**.
-  **Volumetric absorptive microsampling (VAMS)** enables finger-prick blood collection.

Current limitations

-  Often associated with high rates of **adverse events**¹.
-  TDM currently relies on time-intensive, in-clinic venous blood sampling.
-  Established **toxicity thresholds** are **serum-based**².

Objectives

-  How can VAMS-based CABO samples be reliably **translated into serum exposure**?
-  Can VAMS-based serum C_{min} **inform toxicity risk** assessment?

Methods

Clinical data (prospective)



ON-TARGET:

25 patients

- 230 C_{serum}

- 87 C_{VAMS} of 12 patients



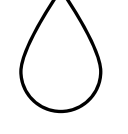
UKW Study:

18 patients

- 41 C_{serum}

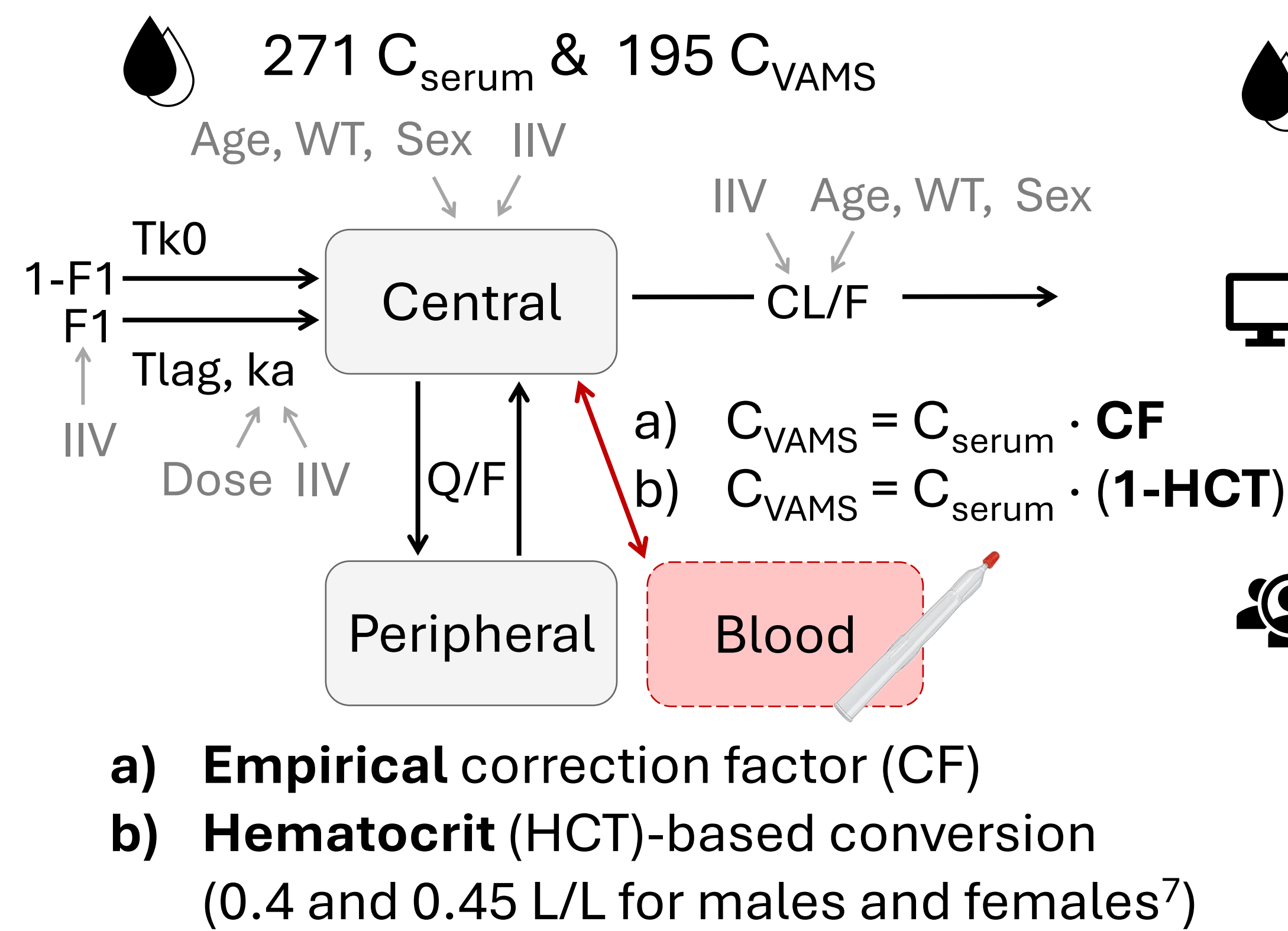
- 108 C_{VAMS}

1 Serum base model

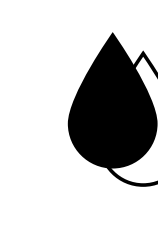
 271 C_{serum}

External evaluation of 4 published CABO NLME models³⁻⁶

2 Conversion model



3 TDM setting & toxicity risk

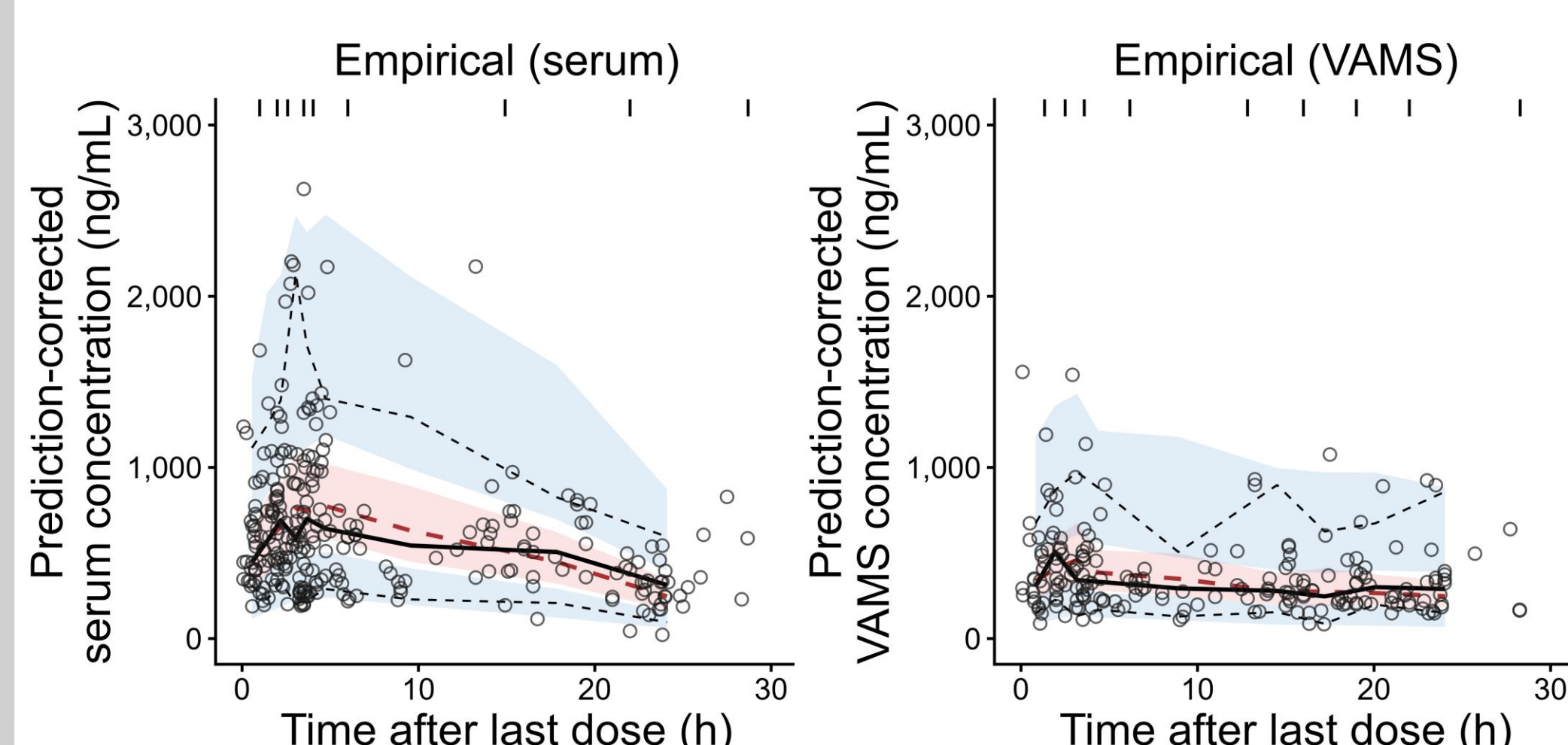
-  117 serum-VAMS pairs at steady state of 30 patients.
-  **Iterative** predictive performance assessment comparing **C_{min} predictions**.
-  **Toxicity risk** classification using established threshold of $C_{min} = 617.7 \text{ ng/mL}$.

Results (model extension)

1 Increased CL/F in serum model

Parameter	Tran <i>et al.</i> ⁶	Re-estimation	
		Estimate	RSE (%)
CL/F (L/h)	2.18	3.48	8.2
RUV (CV, %)	37.5	34.7	8.0
dOFV		-39.9	
MDAPE (%)	61.5	38.2	
MAIPE (%)	19.1	19.4	

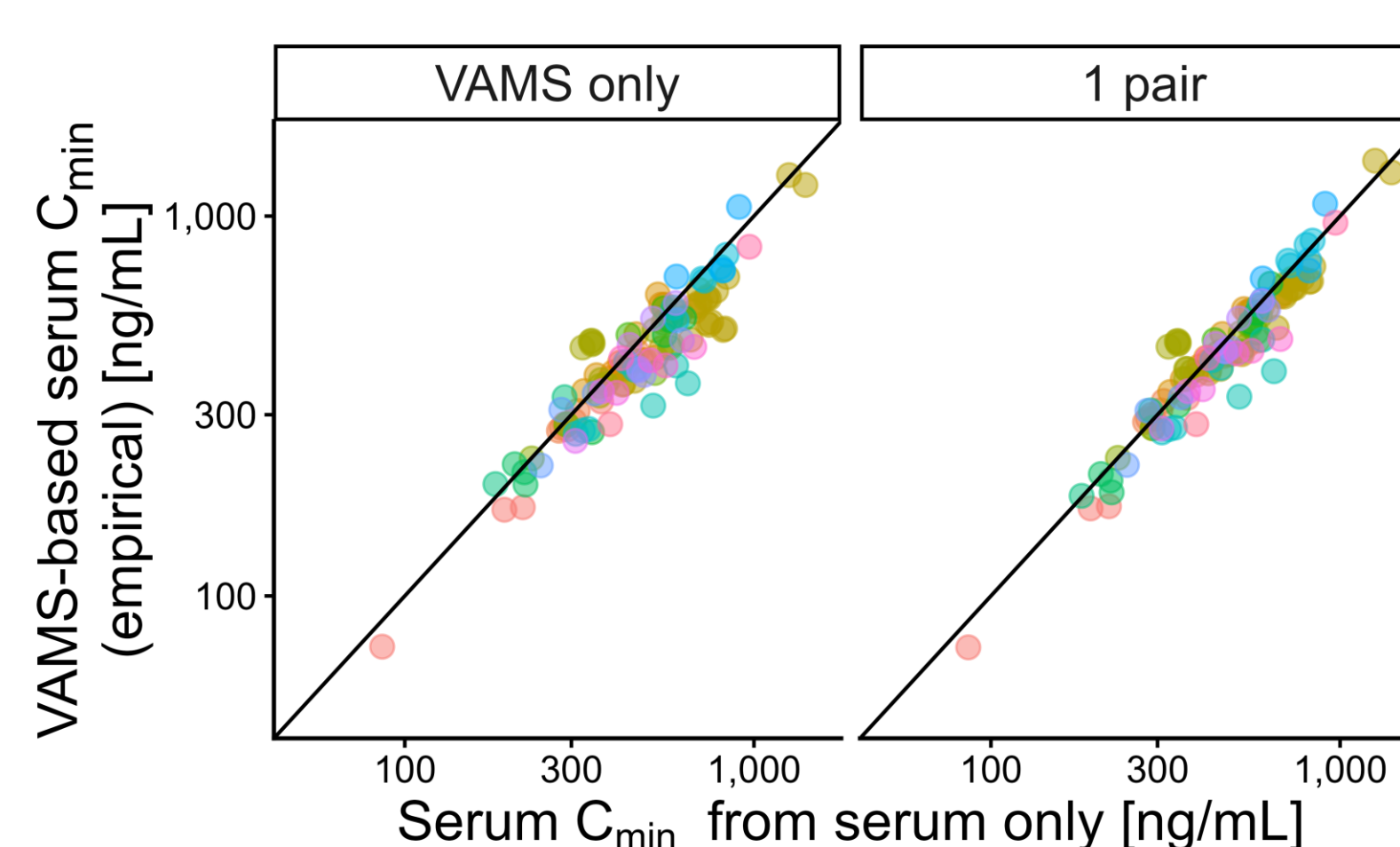
2 Adequate matrix-specific predictions



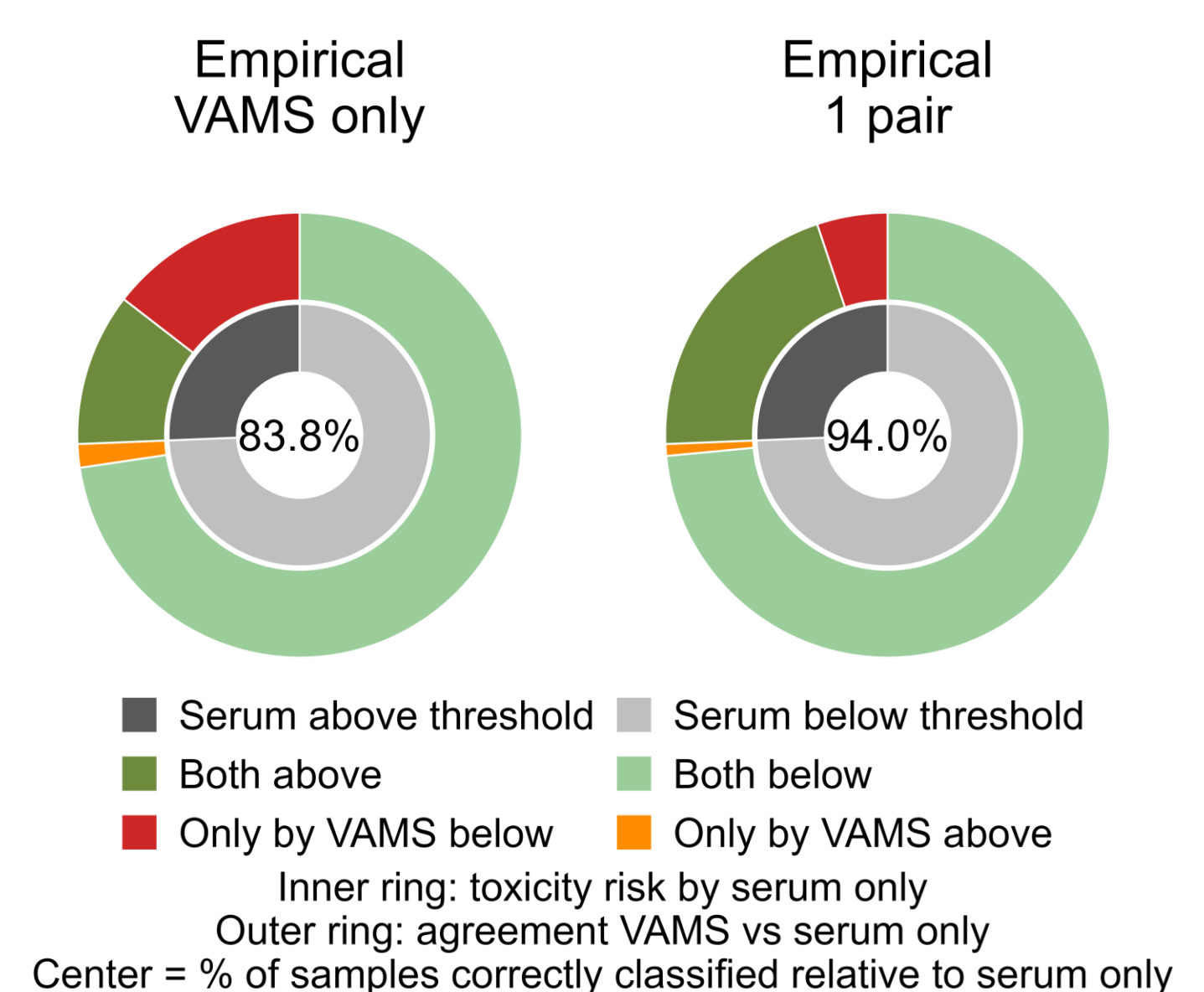
Similar serum predictions by conversion via empirical CF of 0.615 (5% RSE) and HCT

Results (TDM application)

3 Accurate serum exposure prediction by VAMS-based TDM



High concordance in toxicity risk classification



Discussion and conclusion

- ✓ VAMS data were successfully translated into serum predictions.
- ★ Potential to reduce patient burden and support flexible TDM.
- ? Unclear effect of high hematocrit variability on conversion performance.
- ? Promising performance warrants confirmation in external validation.

VAMS-based TDM informed toxicity risk accurately, further improved by one additional serum sample.

References:

- [1] Schmidinger *et al.*, The Oncologist, 2018.
- [2] Cerbone *et al.*, ESMO Open, 2021.
- [3] FDA, Clinical Pharmacology and Biopharmaceutics Review for Cabometyx, 2016.
- [4] Lacy *et al.*, Cancer Chemother. Pharmacol. 2018.
- [5] Nguyen *et al.*, J. Clin. Pharmacol., 2019.
- [6] Tran *et al.*, Cancer Chemother. Pharmacol., 2023.
- [7] Van Erp *et al.*, Clin. Pharmacokinet., 2016

Abbreviations: C_{min} , Minimal concentration; MDA(I)PE, median absolute (individual) prediction error; RSE, relative standard error; RUV, residual unexplained variability; TDM, therapeutic drug monitoring.

Talk to the author

Chrisoula Tahtsidou
c.tahtsidou@lmu.de

website



contact

