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Introduction

- Cabozantinib is approved for the treatment of metastatic renal cell carcinoma (mRCC) at a **60-mg oral daily dose**^[1].
- However, the registered dose of 60 mg once daily is not well tolerated in patients.** Additionally, increasing cabozantinib exposure showed to **not be associated with improved outcome**^[2].
- Cabozantinib expenses are estimated to be €6,200 per patient per month and a flat pricing model is applicable for all available strengths.**
- Hence, PK-PD studies in real-world patients are warranted to **explore more tolerable and costs-saving regimens** with comparable efficacy.

Objectives

- To evaluate the performance of a previously published population pharmacokinetic (PopPK) model of cabozantinib reported in the FDA registration documents (FDA model) with real-world patients' therapeutic drug monitoring (TDM) data^[3].
- To explore alternative costs-saving dose regimens with similar drug exposure.

Methods

Dataset:

- 27 mRCC patients with 75 cabozantinib observations.

Model optimization procedures:

- The structural and statistical components of the model were adopted from the FDA model:
 - At first, all parameters were fixed to the reported values^[3].
 - Apparent clearance (CL) was estimated.

Population PK modeling and simulations:

- Software:** NONMEM® 7.4.4., R 4.1.3.
- Model comparison criteria:** Goodness of fit (GOF) plots and stratified GOF for dose and other characteristics.
- Model validation:** Bootstrap and NPDE.

- Simulations:** 1000 Monte Carlo simulations were performed using the model with estimated CL (Table 2). A scenario (40 mg qd versus 2 days 60 mg followed by 1 rest day, Figure 3) was simulated to explore the alternative costs-saving dose regimen.

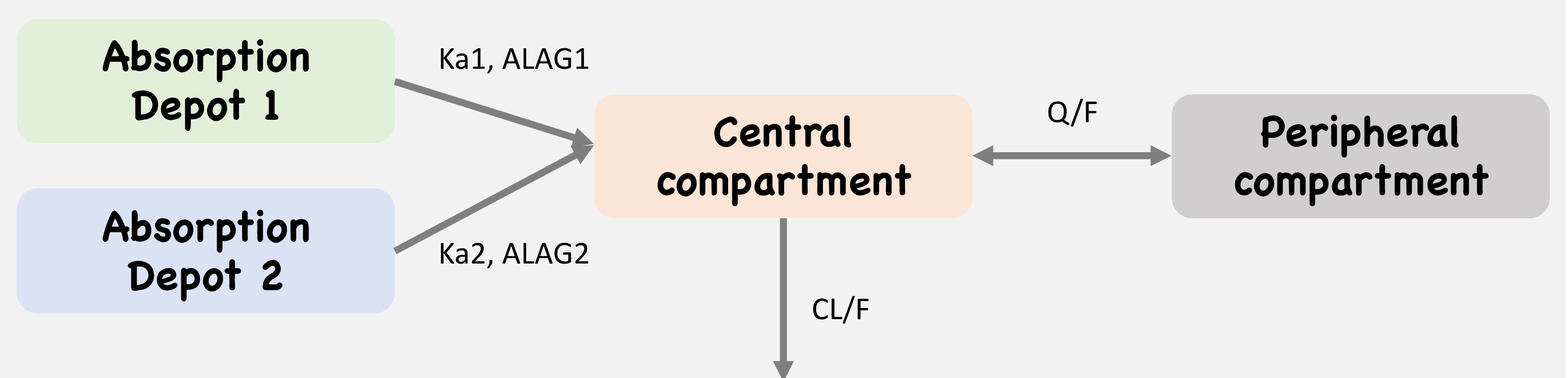


Figure 1. Schematic representation of the FDA model of cabozantinib

Results

- 27 patients with 75 TDM observations treated at the Leiden University Medical Centre (LUMC) were identified (Table 1).

Table 1. Characteristics (median (range)) of included cabozantinib patients (n=27)

Characteristics	Results
Age (years)	65 (39 - 85)
Body weight (kg)	79.0 (49.4 - 105)
Height (cm)	178 (160-196)
Gender	70.3% male

- Table 2 shows the parameter values of the model (Figure 1).
- Cabozantinib TDM concentrations (DV) were **generally adequately predicted** by the developed model (Figure 2).
- The estimated CL was **slightly higher than previously reported** (2.84 L/h vs. 2.23 L/h).

Table 2 The PK parameters results of the FDA model (all fixed to FDA report except CL)

Parameters	Value	Parameters	Value
CL (L/h)	2.84	ALAG1 (h)	0.459 FIX
F1 (/)	0.675 FIX	Ka2 (h)	0.102 FIX
V2 (L)	81.5 FIX	ALAG2 (h)	16.8 FIX
V3 (L)	213 FIX	ω^2_{CL}	0.213 FIX
Q (L/h)	14.2 FIX	ω^2_{V2}	1.06 FIX
Ka1 (h)	0.568 FIX	ω^2_{Ka}	0.437 FIX

- Bootstrap and NPDE indicated normal distribution and reasonably symmetrical.
- Simulations indicate that 40 mg qd versus 2 days 60 mg followed by 1 rest day (Figure 3) could have **a similar AUC_{72h} when in steady state (92,380 vs. 95,400 ng·h/mL) with 33% costs reduction** (Figure 4).

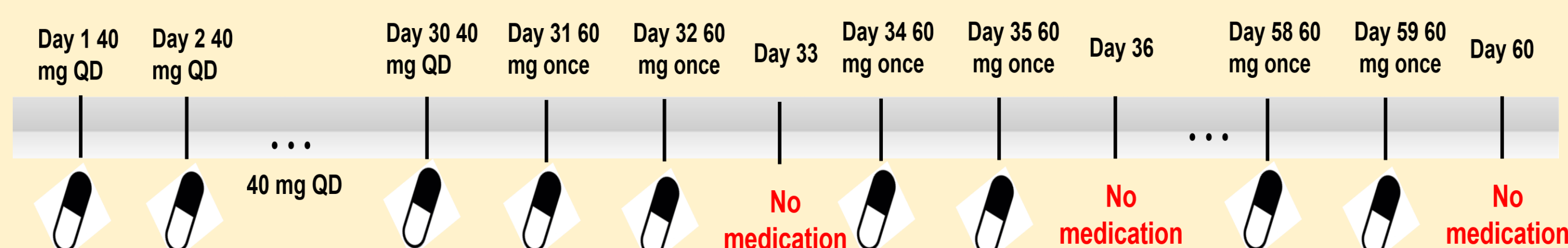


Figure 3. The medication scheme of the simulation scenario for alternative dosing regimen

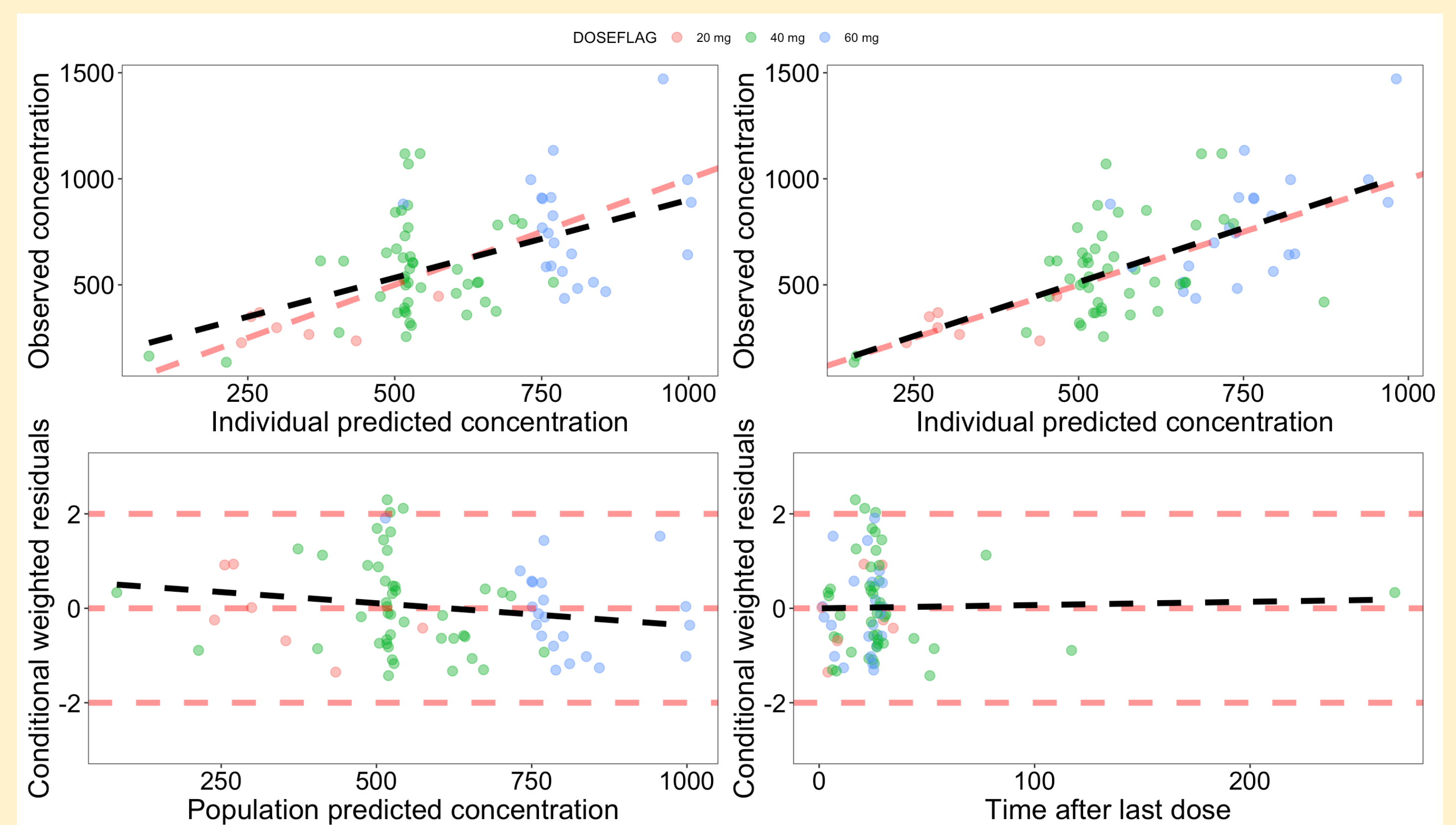


Figure 2. GOF plots of the FDA model (CL estimated)

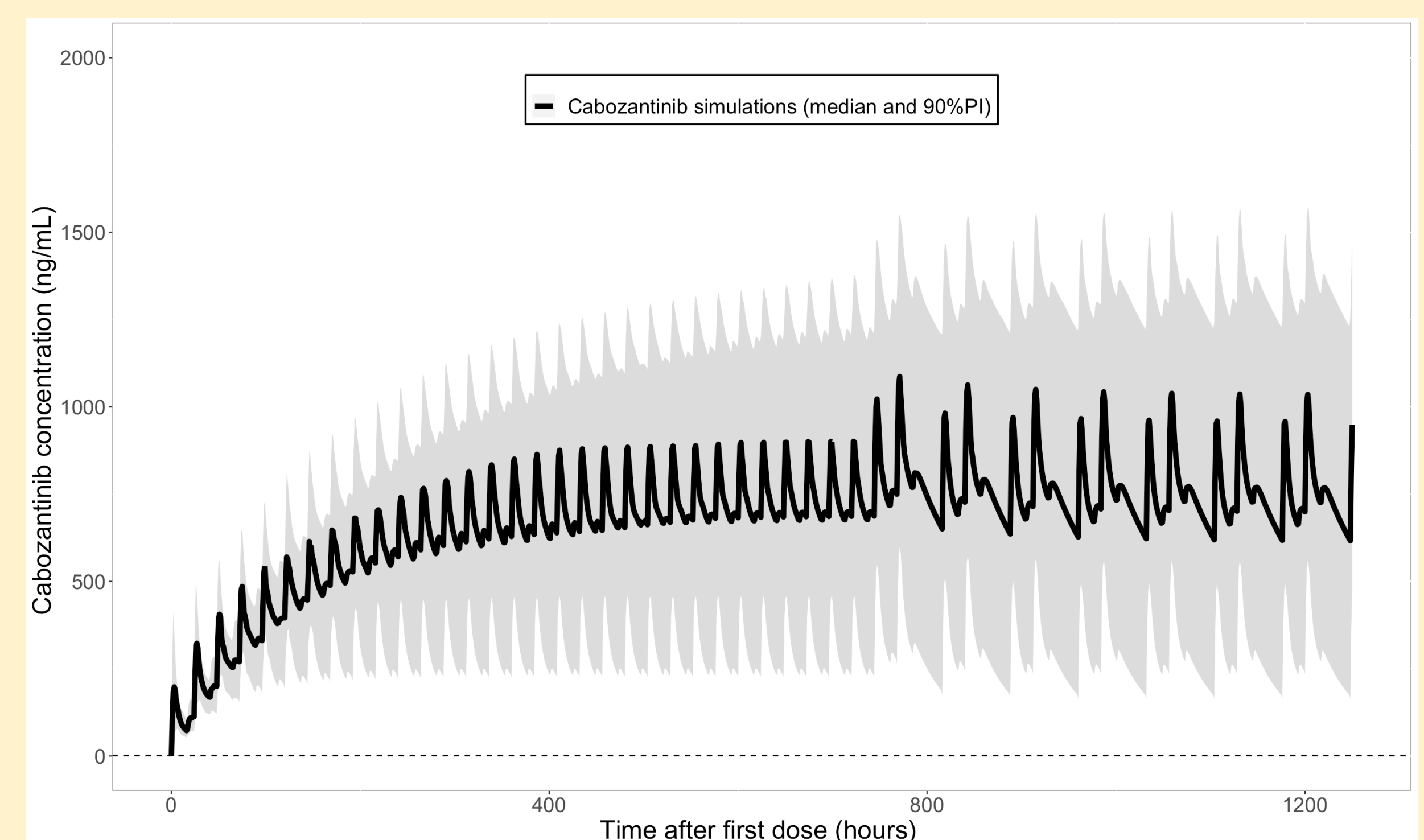


Figure 4. Model-based simulations (CL estimated)

Conclusions and Perspectives

- Application of a previously published model with estimated CL results in generally adequate prediction for the real-world cabozantinib TDM data.
- A promising costs-saving regimen that could save 33% of the cabozantinib expenses was developed which warrants clinical validation.
- Ultimately, these PK observations will be combined with PD outcomes to explore PK-PD relation of cabozantinib in real-world mRCC patients.

References:

- [1] Lacy SA et al. Clin Pharmacokinet (2017) 56 (5), 477-491.
- [2] Krens SD et al. BMC Cancer (2022) 22 (1), 228.
- [3] CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S) OF CABOMETYX (2015). FDA.

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