

Population pharmacokinetics of cobicistat in once and twice daily regimens in various populations

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Introduction

- **Cobicistat** is a selective, mechanism-based inhibitor of the cytochrome P450 (CYP) 3A-enzyme.¹
- Cobicistat is approved for pharmacokinetic (PK) boosting of CYP3A-substrates in patients with HIV.
- **PK boosting** has gained interest in other populations to reduce financial toxicity and pill burden.²
- Different patient populations could show altered cobicistat PK due to differences in disposition, interaction potential of comedication, and dose.

Objective: To describe the PK of once and twice daily cobicistat regimens in various subject groups.

Methods

PK data from four clinical trials was pooled (see **Table 1**). All trials performed dense PK sampling at steady state.

Table 1. Data collection

Trial	N	Samples	Dose ^a	Indication	Comedication
DATE-4 ³	16	184	QD	Healthy volunteers	Atazanavir Daclatasvir
PANNA ⁴	12	116	QD	HIV, postpartum	Elvitegravir Emtricitabine TAF or TDF
PRACTICAL ⁵	26	154	QD	Rheumatoid arthritis	Tofacitinib
PROACTIVE-A ⁶	12	260	BID	Solid tumours	Olaparib
Total	66	684			

^a All patients received a dose of 150 mg. QD, once daily; BID, twice daily; HIV, Human Immunodeficiency Virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

Conventional compartmental (CM) and mechanistic well-stirred liver models (WSLM) were evaluated.

- Allometric scaling
 - To total body weight for absorption rate constant (both models), volume of distribution (both) and clearance (CM).
 - To liver volume, scaled to total body weight, for intrinsic clearance (WSLM).⁷
- WSLM assumptions: cobicistat fraction unbound 0.025¹, liver blood flow 90 L/hour⁸, and haematocrit 0.44⁹.

Concurrent use of atazanavir, tofacitinib and olaparib/twice daily dosing were evaluated as covariates on bioavailability and apparent oral clearance or intrinsic clearance. Covariates were selected on physiological plausibility and statistical significance ($p < 0.05$, $dOFV < -3.84$) of the estimated effect. Analysis was performed with NONMEM 7.5.1 and Rstudio 4.1.3 with the package Xpose4 4.7.3.

Results

The well-stirred liver model with one central compartment and Erlang type absorption best described cobicistat PK (see **Figure 1**). A combined proportional and additive model for residual error was used.

- No plausible covariates could be identified (see **Table 2**).
- Final model did not include covariates (see **Table 3**, **Figure 2**).

Table 2. Results from the covariate analysis versus expected effect

Covariate	Estimate	Expected effect	Physiological mechanism of the expected effect
Atazanavir	On F_1 ^a 0.90	> 1	CYP3A-inhibition
	On Cl_{int} ^b 1.39	< 1	
Tofacitinib	On F_1 ^a 1.33	= 1	No difference
Olaparib	On F_1 ^a 0.69	> 1	CYP3A-inhibition and twice daily dosing with saturable clearance
	On Cl_{int} ^b 1.21	< 1	

^a Typical $F_1 = 1 \cdot \text{THETA}(X)^{\text{COVARIATE}}$

^b Typical $Cl_{int} = \text{THETA}(3) \cdot \text{THETA}(X)^{\text{COVARIATE}}$

Figure 1. Final Structural Model

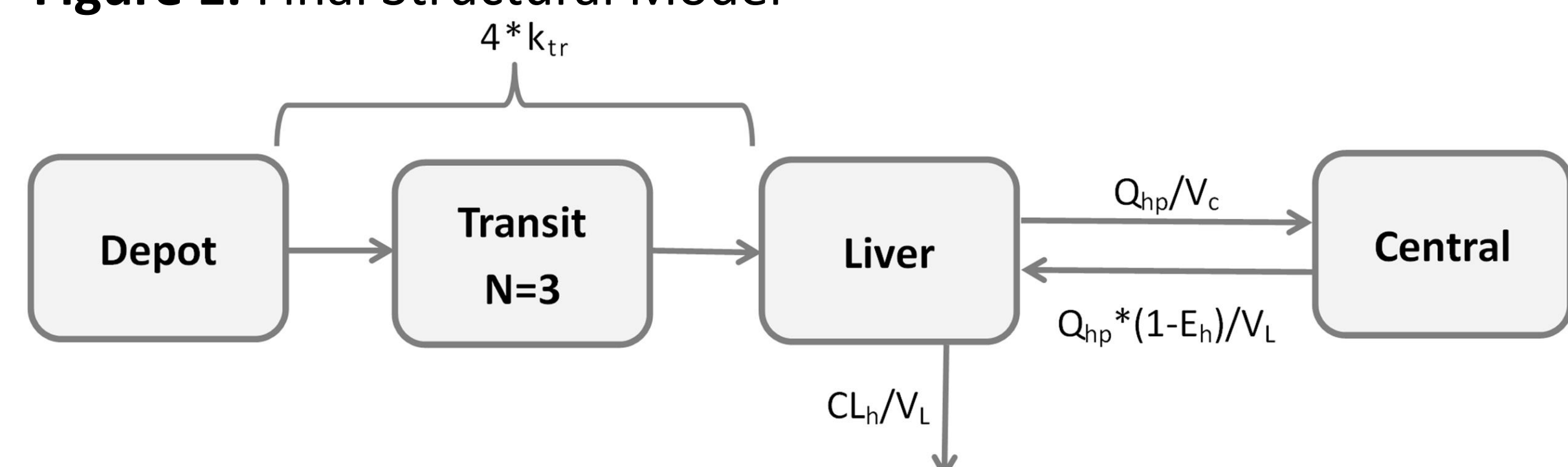
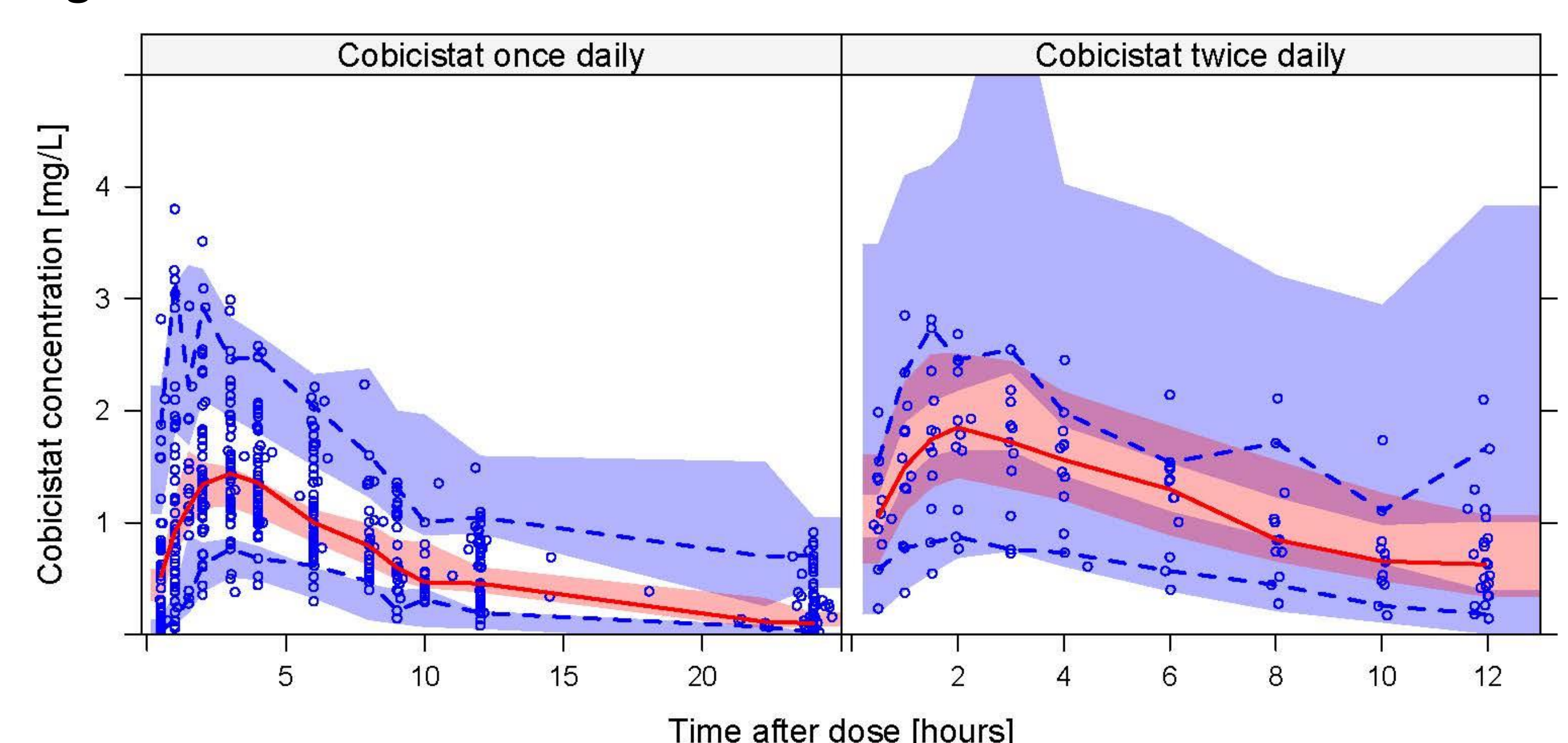


Table 3. Parameter estimates

		Estimate	RSE (%)
THETA	K_{tr} (h^{-1})	4.09	10
	V_c (L)	71.7	7
	Cl_{int} ($l \cdot h^{-1} \cdot L_{liver}^{-1}$)	333	6,5
ETA	K_{tr}	0.381	20.4
	V_c	0.174	19.3
	Cl_{int}	0.213	22.2
SIGMA	Proportional	0.0301	6.2
	Additive	0.0011	26.5

Figure 2. Visual Predicted Check of the final model.



The open circles represent observations. The lines show the median (solid red), 5th and 95th percentiles (dashed blue) of the observations. The shaded areas show the 95% confidence interval around the median (red), 5th and 95th percentiles (blue) of the simulated data.

Discussion

- No plausible effect of concurrent use atazanavir, tofacitinib, olaparib or twice daily dosing could be identified on cobicistat bioavailability or clearance.
- Well-stirred liver model adequately described cobicistat PK for further exposure-response modelling.

This well-stirred liver model is a useful tool to evaluate cobicistat PK and its influence on other drugs



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