Building and Evaluation of a PBPK Model for COMPOUND in Adults

Version	**0.1**
OSP Version	8.0
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1 Introduction

Clarithromycin is a widely prescribed macrolide antibiotic and a substrate and mechanism-based inactivator of CYP3A4. Furthermore, clarithromycin is a substrate and inhibitor of P-gp and an inhibitor of OATP1B1 and OATP1B3 (Eberl 2007, Seithel 2007). Clarithromycin has been proposed as one of the best alternative CYP3A4 inhibitors for clinical DDI studies to avoid further use of ketoconazole.

The presented Clarithromycin model was developed by Moj et al. (Moj 2017) and revised by Hanke et al. (Hanke 2018).

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. (Kuepfer 2016). Information regarding the relevant anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in adults was gathered from the literature and has been previously published (PK-Sim Ontogeny Database Version 7.3). The information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available PK-Sim® Ontogeny Database Version 7.3 (Schlender 2016) or otherwise referenced for the specific process.

The clarithromycin model was developed using 17 clinical studies, covering a dosing range from 100 to 1200 mg. The model applies partitioning into blood cells, metabolism by CYP3A4 including mechanism-based auto-inactivation and a renal clearance.

Unknown parameters (see below) were identified using the Parameter Identification module provided in PK-Sim®.

The model was then verified by simulating:

- ...

Details about input data (physicochemical, *in vitro* and clinical) can be found in Section 2.2.

Details about the structural model and its parameters can be found in Section 2.3.

2.2 Data

2.2.1 In vitro / physico-chemical Data

A literature search was performed to collect available information on physiochemical properties of dapagliflozin. The obtained information from literature is summarized in the table below.

Parameter	Unit	Value	Source	Description
MW	g/mol	747.95		Molecular weight
pK_a		8.99 (base)	McFarland 1997	Acid dissociation constant
Solubility (pH)	mg/L	12170 (2.4)	Salem 2003	Solubility
logP		2.3	Lappin 2011	Partition coefficient between octanol and water
fu	%	28.0, 30.0, 40.0	Davey 1991 , Chu 1993a, Noreddin 2002	Fraction unbound in plasma
CYP3A4 Km	µmol/L	48.7	Rodrigues 1997	Michaelis-Menten constant
CLren	mL/min	110-213	Rodvold 1999	Renal plasma clearance

Parameter	Unit	Value	Source	Description
CYP3A4 Ki	µmol/L	2.25, 4.12, 5.49, 29.5, 39.2	Polasek 2006, Jones 2007, Mayhew 2000, Ito 2003	Conc. for half-maximal inactivation
CYP3A4 kinact	1/min	0.04, 0.05, 0.07, 0.23	Polasek 2006, Jones 2007, Mayhew 2000, Ito 2003	Maximum inactivation rate
P-gp Ki	µmol/L	4.1	Eberl 2007	Conc. for half-maximal inhibition

2.2.2 Clinical Data

A literature search was performed to collect available clinical data on clarithromycin in healthy adults.

2.2.2.1 Model Building

The following studies were used for model building (training data):

Publication	Arm / Treatment / Information used for model building
Chu 1992a	Healthy subjects with intravenous administration (0.75 h) of 250 mg
Chu 1993	Healthy subjects with oral administration of 250 or 500 mg as single or twice daily for 5 days

2.2.2.2 Model Verification

The following studies were used for model verification:

Publication	Arm / Treatment / Information used for model building
Chu 1992	Healthy Subjects with single doses between 100-1200 mg
Kees 1995	Healthy subjects with oral administration of 250 or 500 mg as single or multiple dose
Rengelshausen 2003	Oral administration of 250 mg twice a day for 1.5 days
Abduljalil 2009	Oral administration of 500 mg twice a day for 3.5 days

2.3 Model Parameters and Assumptions

2.3.1 Absorption

...

2.3.2 Distribution

...

After testing the available organ-plasma partition coefficient and cell permeability calculation methods built in PK-Sim, observed clinical data was best described by choosing the partition coefficient calculation by `Rodgers and Rowland` and cellular permeability calculation by `PK-Sim Standard`.

...

2.3.3 Metabolism and Elimination

...

2.3.4 Automated Parameter Identification

This is the result of the final parameter identification.

Model Parameter	Optimized Value	Unit
`PK-Sim parameter 1`		
`PK-Sim parameter 2`		
`PK-Sim parameter 3`		
`PK-Sim parameter 4`		

3 Results and Discussion

The PBPK model for COMPOUND was developed and verified with clinical pharmacokinetic data.

The model was evaluated covering data from studies including in particular

- ...
- ...

The model quantifies ...

The next sections show:

1. the final model parameters for the building blocks: Section 3.1.
2. the overall goodness of fit: Section 3.2.
3. simulated vs. observed concentration-time profiles for the clinical studies used for model building and for model verification: Section 3.3.

3.1 Final input parameters

The compound parameter values of the final PBPK model are illustrated below.

Compound: Clarithromycin

Parameters

Name	Value	Value Origin	Alternative	Default	
Solubility at reference pH	12.17 mg/ml		Measurement	True	
Reference pH	2.4		Measurement	True	
Lipophilicity	2.3 Log Units		Measurement	True	
Fraction unbound (plasma, reference value)	0.299		Measurement	True	
Specific intestinal permeability (transcellular)	1.23E-06 dm/min		fit	True	
Is small molecule	Yes				
Molecular weight	747.9534 g/mol				
Plasma protein binding partner	Albumin				

Calculation methods

Name	Value	
Partition coefficients	Rodgers and Rowland	
Cellular permeabilities	PK-Sim Standard	

Processes

Metabolizing Enzyme: CYP3A4-fit

Molecule: CYP3A4

Parameters

Name	Value	Value Origin	
In vitro Vmax for liver microsomes	0 pmol/min/mg mic. protein		
Km	48.7 µmol/l		
kcat	76.5 1/min	Unknown	

Systemic Process: Renal Clearances-fitted

Species: Human

Parameters

Name	Value	Value Origin	
Body weight	71.5 kg	Unknown	
Blood flow rate (kidney)	1.31 l/min	Unknown	
Fraction unbound (experiment)	0.4		
Plasma clearance	1.75 ml/min/kg		

Inhibition: ABCB1-Eberl (2007)

Molecule: ABCB1

Parameters

Name	Value	Value Origin	
Ki	4.1 µmol/l		

Inhibition: CYP3A4-fitted

Molecule: CYP3A4

Parameters

Name	Value	Value Origin	
kinact	0.04 1/min		
K_kinact_half	6.04 µmol/l		

Inhibition: OATP1B1-Vermeer 2016

Molecule: OATP1B1

Parameters

Name	Value	Value Origin	
Ki	5.3 µmol/l		

Inhibition: OATP1B3-Vermeer 2016

Molecule: OATP1B3

Parameters

Name	Value	Value Origin	
Ki	14 µmol/l		

Formulation: Tablet Clarithromycin

Type: Weibull

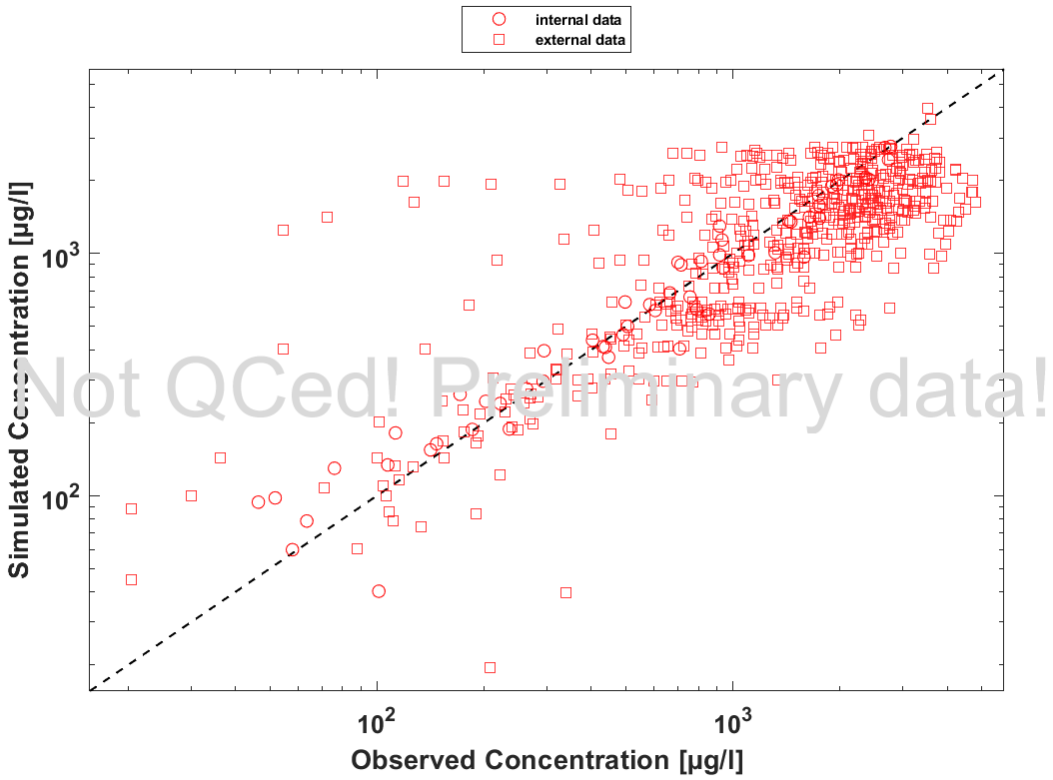
Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	5 min		
Lag time	0 min		
Dissolution shape	2.9		
Use as suspension	No		

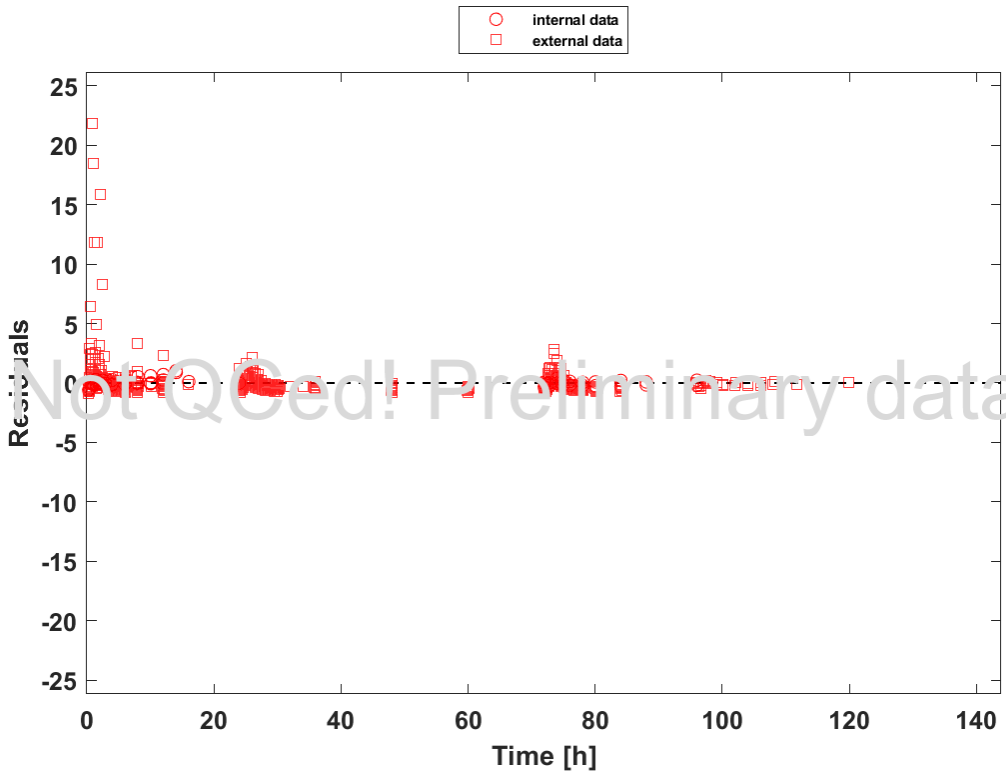
3.2 Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data used presented in Section 2.2.2.

The first plot shows observed versus simulated plasma concentration, the second weighted residuals versus time.



Goodness of fit plor for concentration in plasma



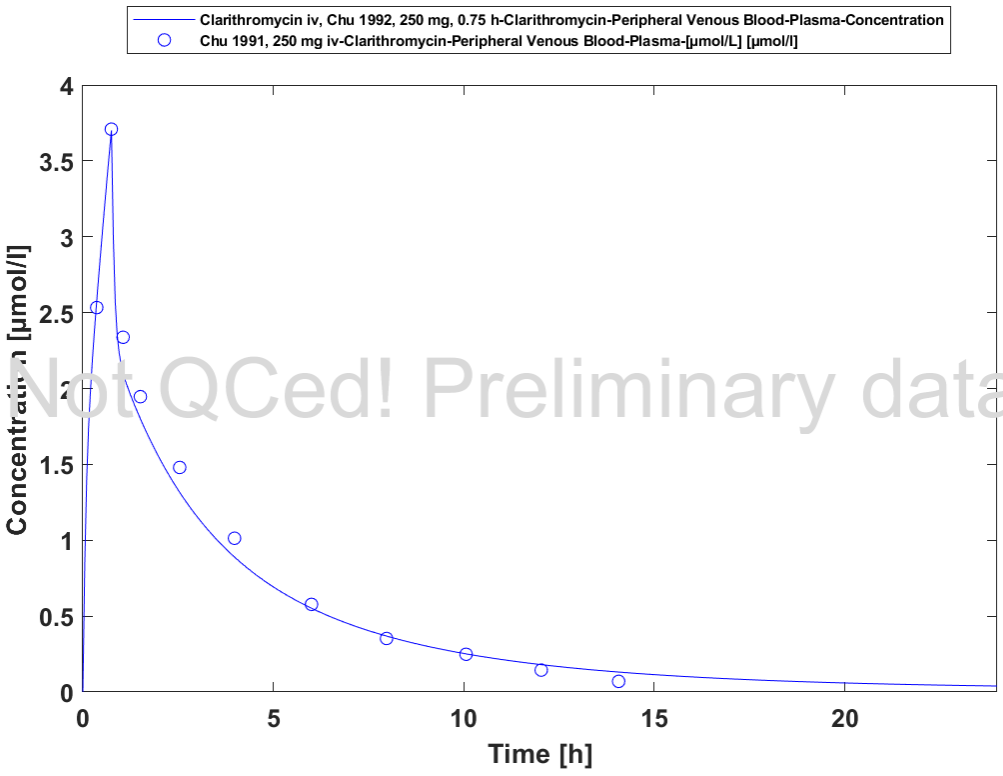
Goodness of fit plor for concentration in plasma

GMFE = 1.575193

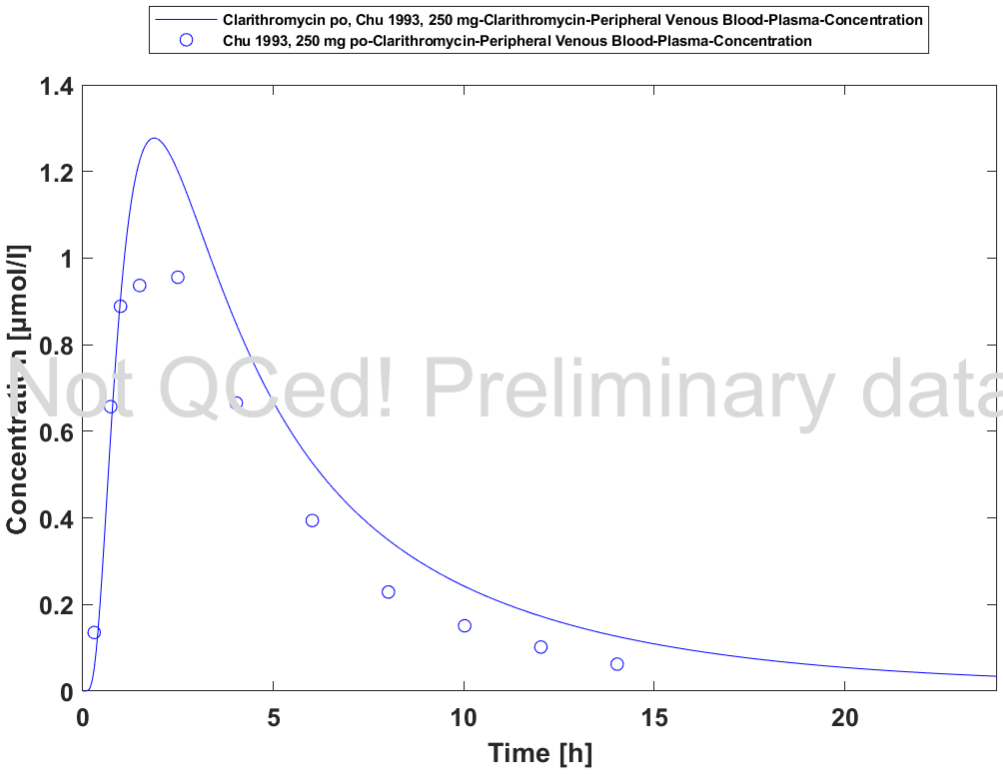
3.3 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in Section 2.2.2 are presented below.

3.3.1 Model Building



Time Profile Analysis



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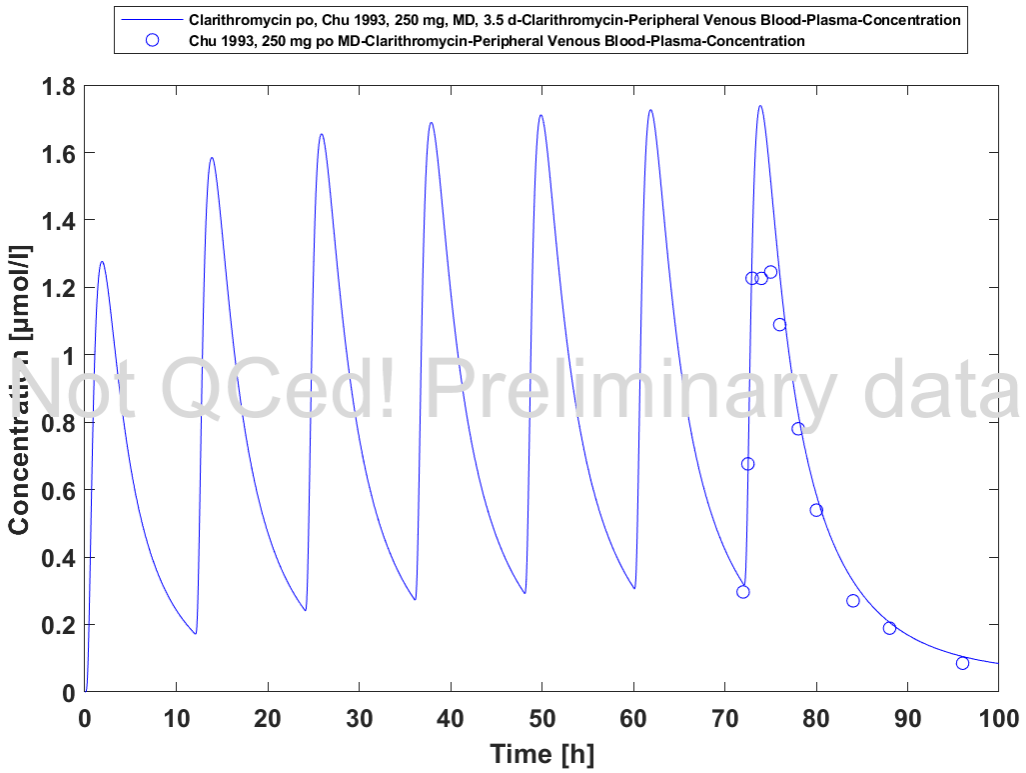

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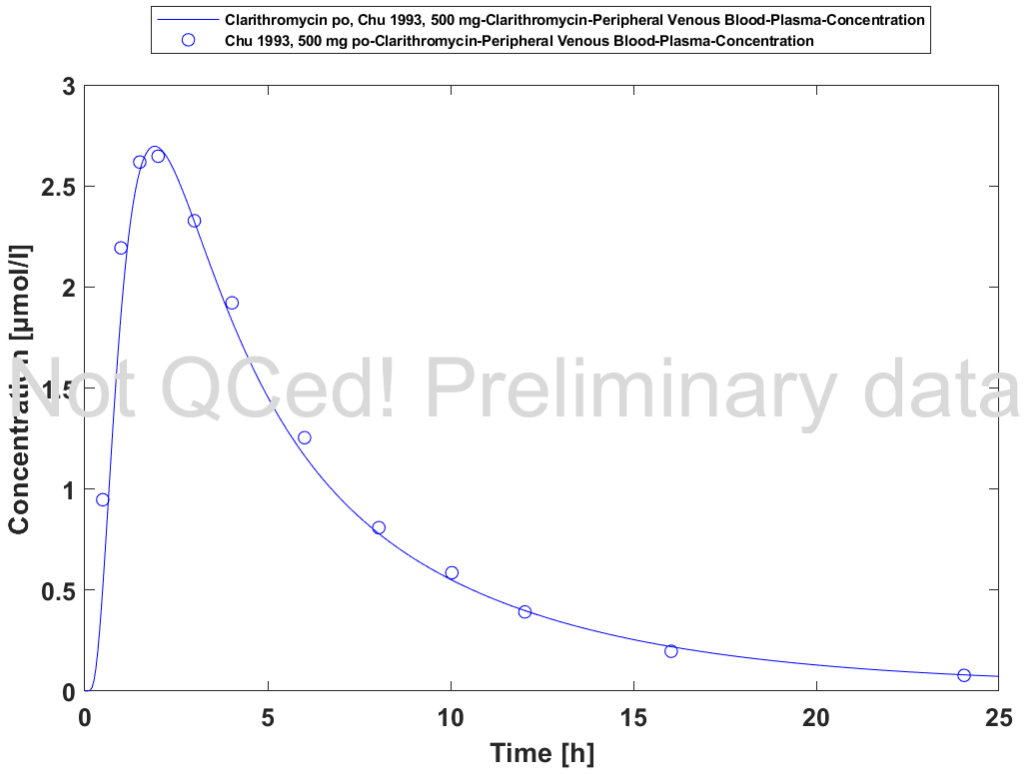

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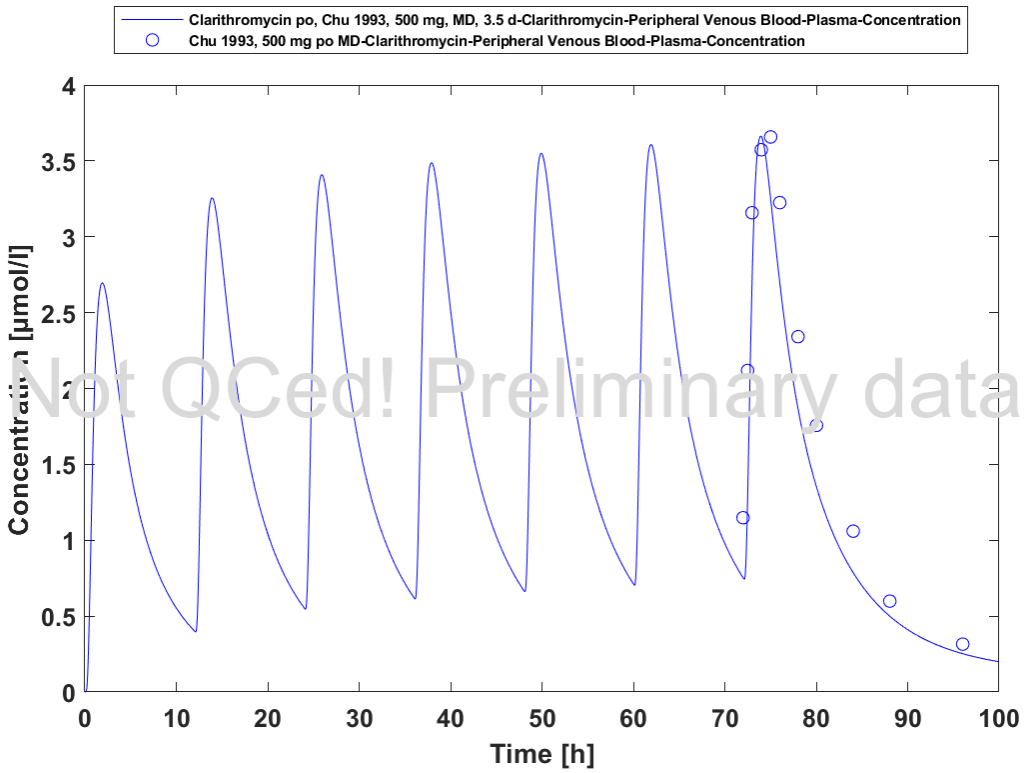
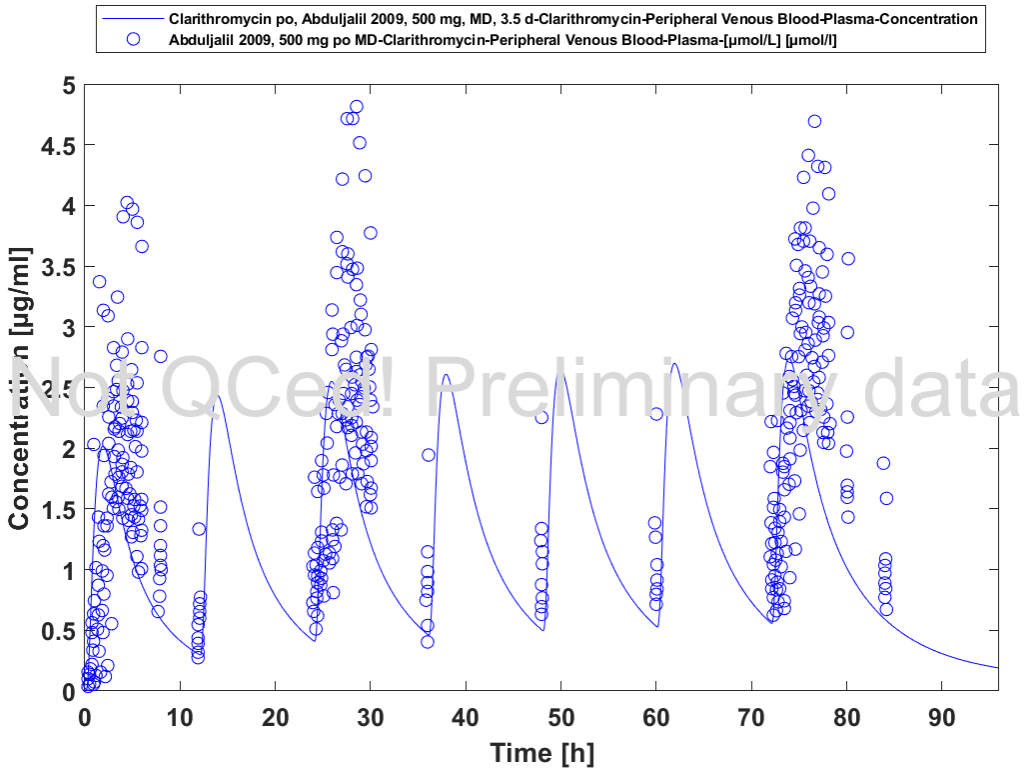


Time Profile Analysis

3.3.2 Model Verification



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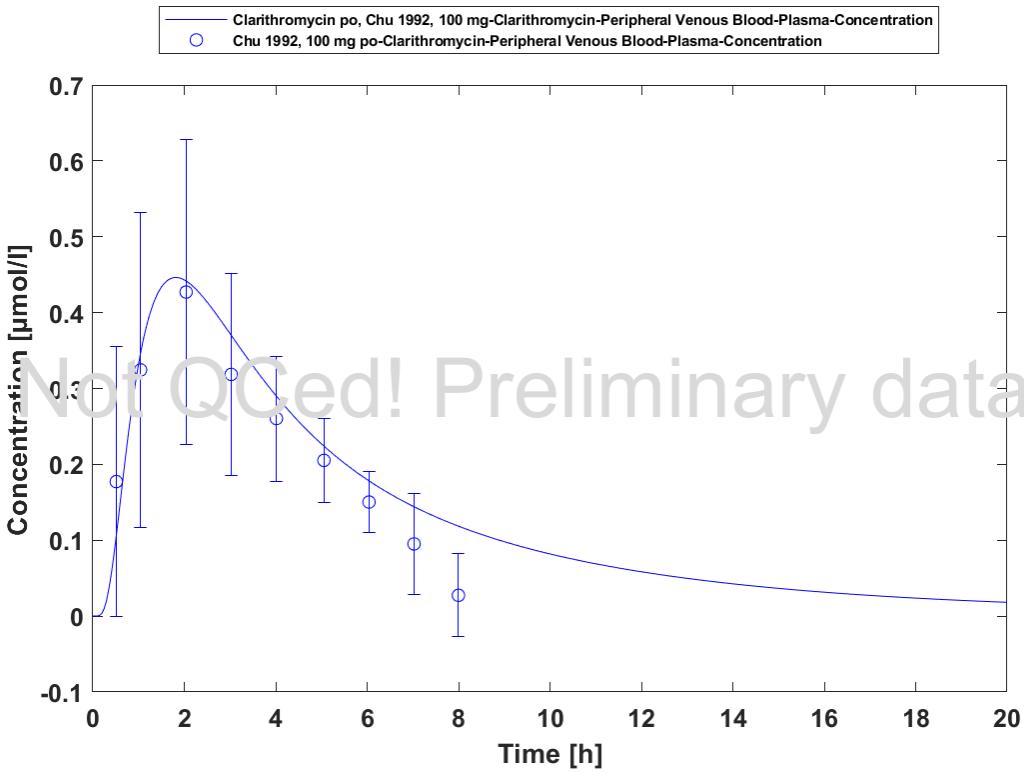

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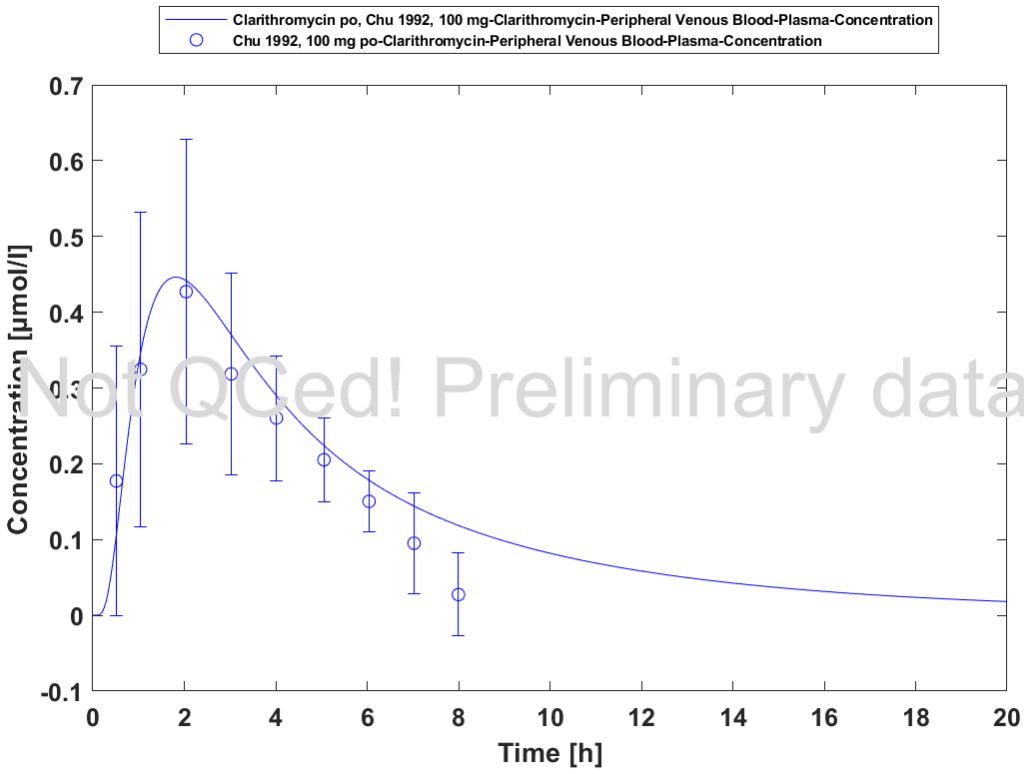

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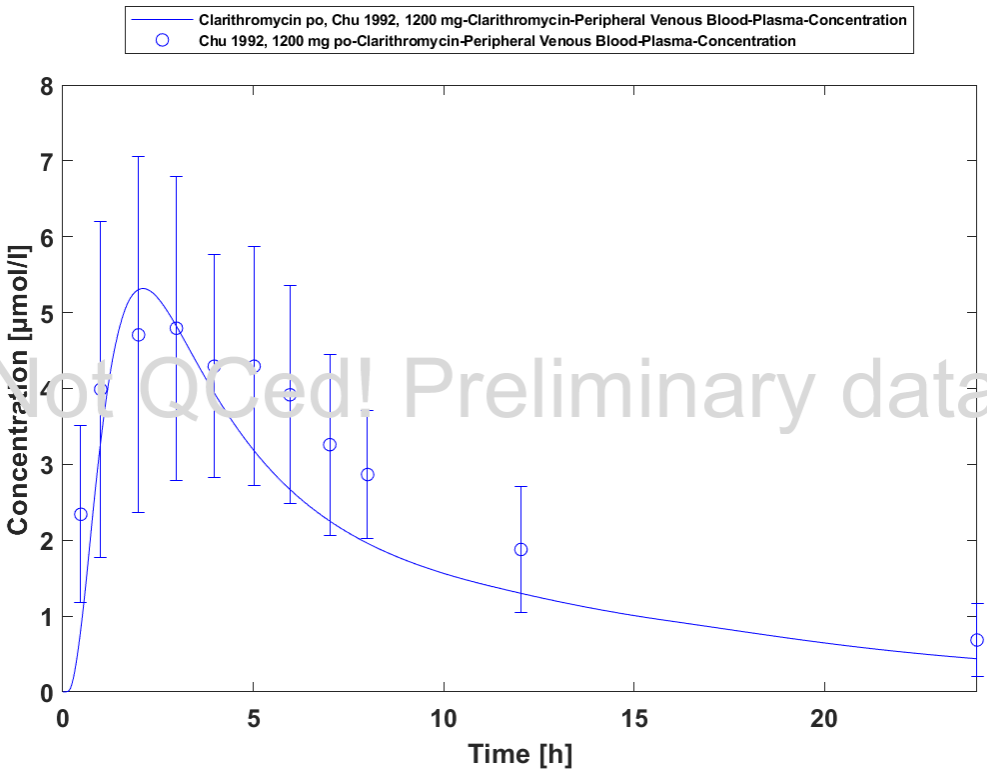

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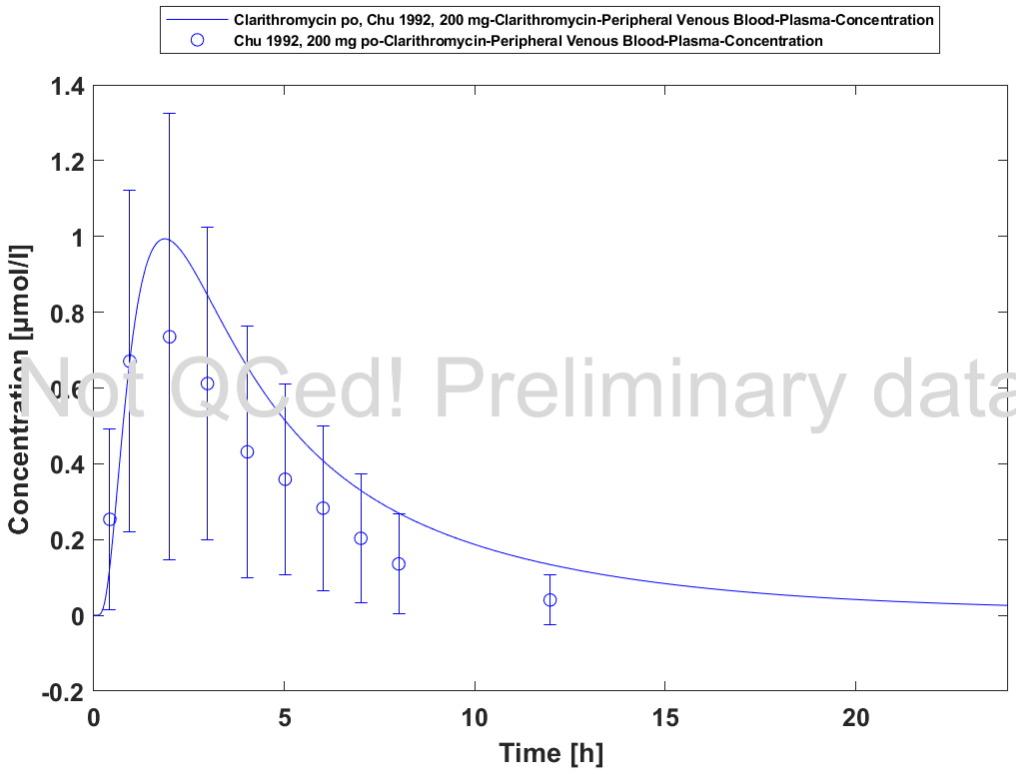

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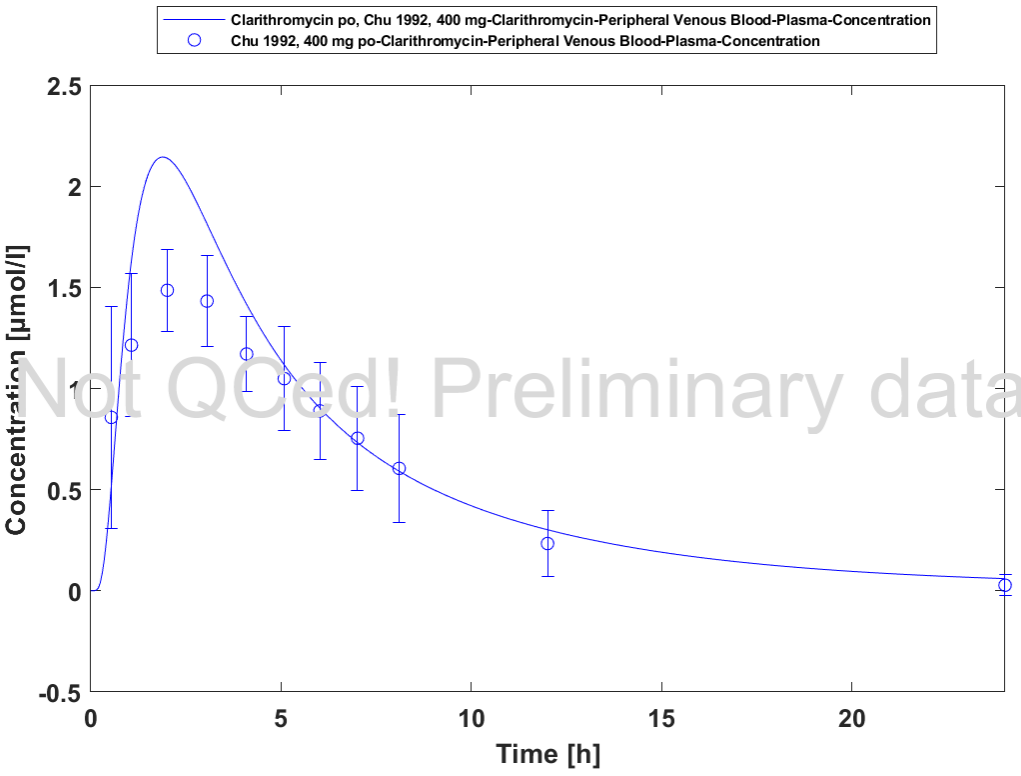

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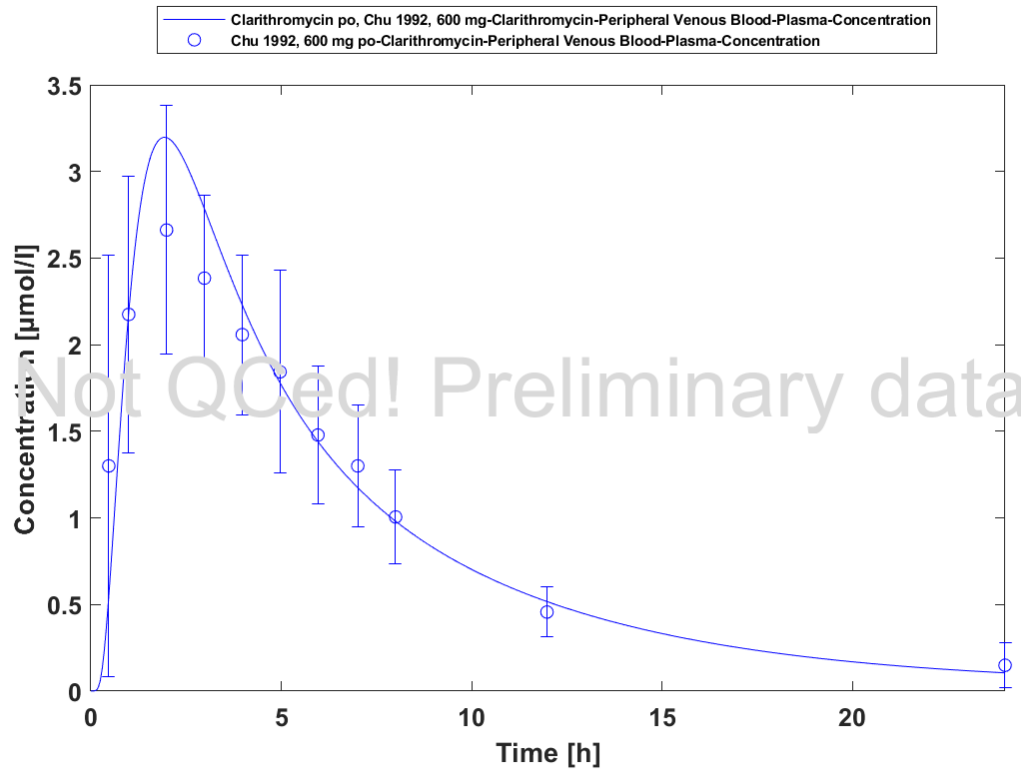

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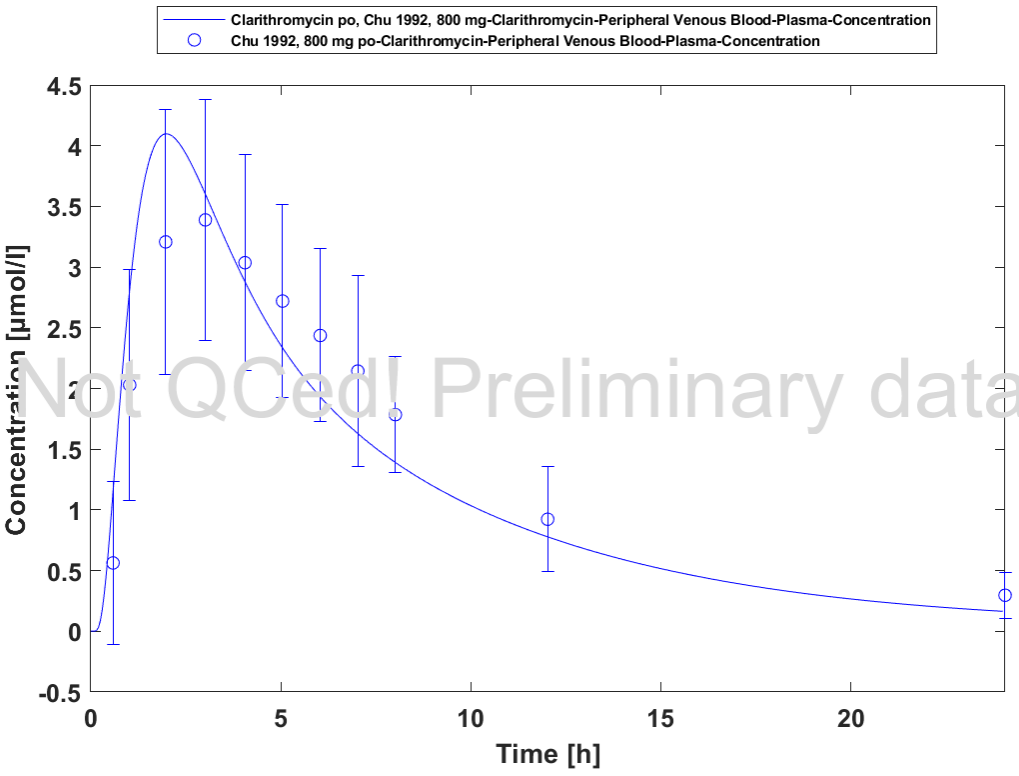

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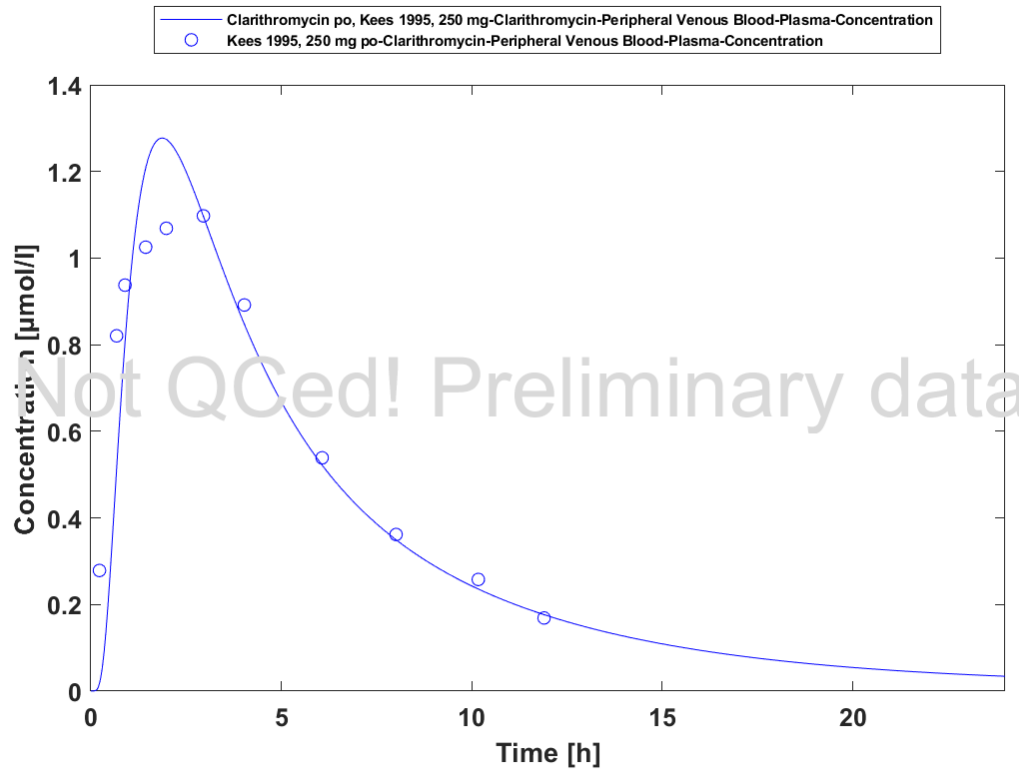

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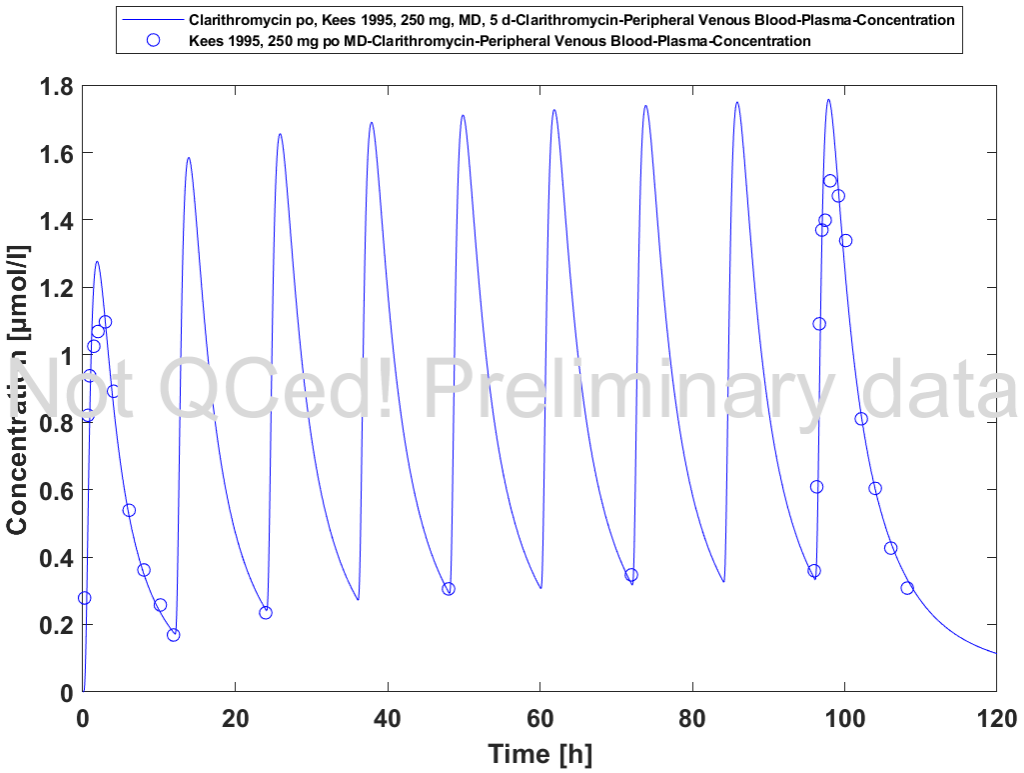

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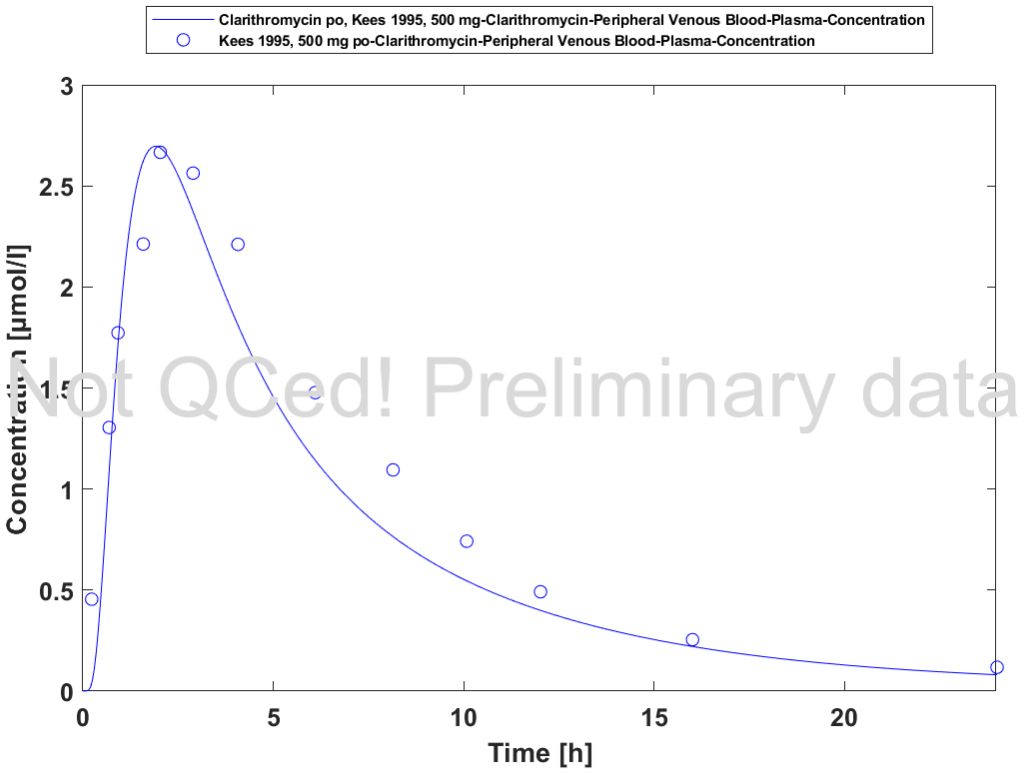

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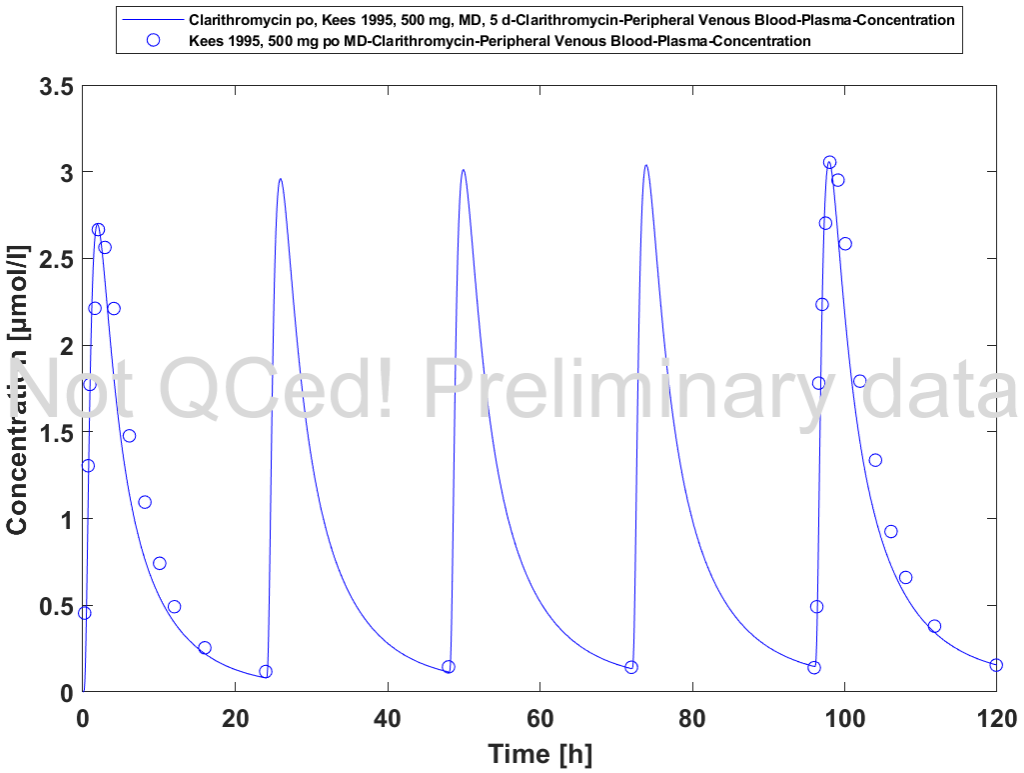

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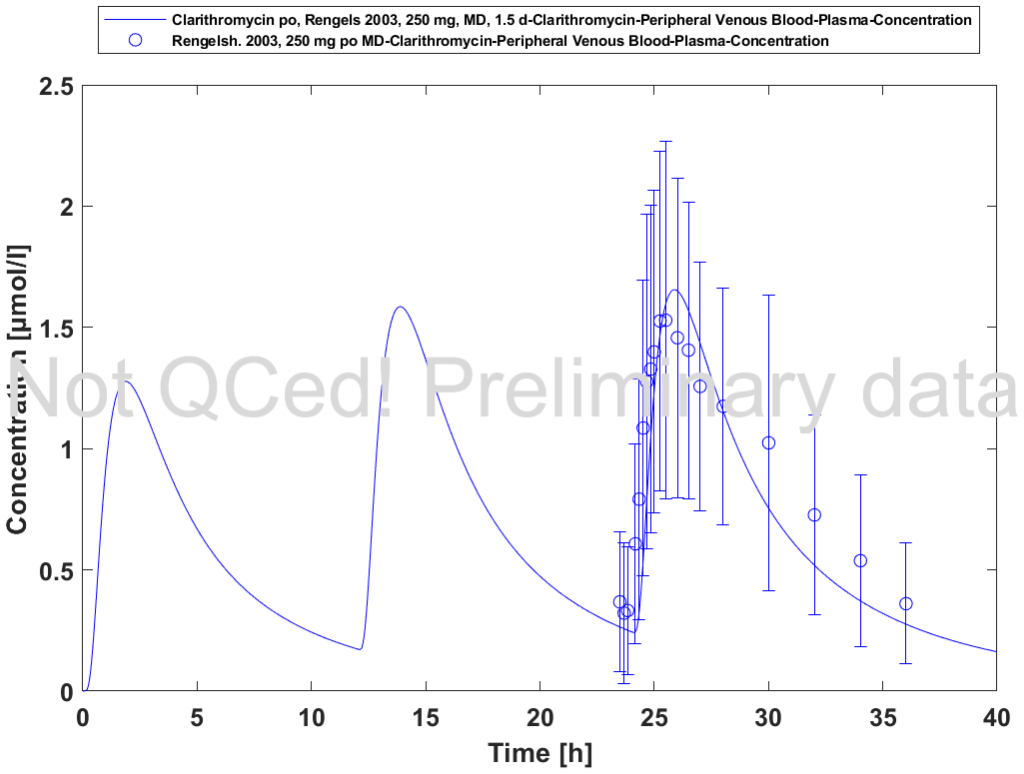

Time Profile Analysis

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of COMPOUND in adults.

In particular, it applies quantitative ... Thus, the model is fit for purpose to be applied for...

5 References

Abduljalil 2009 Abduljalil, K. et al. Modeling the autoinhibition of clarithromycin metabolism during repeated oral administration. Antimicrob. Agents Chemother. 53, 2892–901 (2009).

Chu 1992 Chu, S.Y. et al. Pharmacokinetics of clarithromycin, a new macrolide, after single ascending oral doses. Antimicrob. Agents Chemother. 36, 2447–53 (1992).

Chu 1992a Chu, S.Y., Deaton, R. & Cavanaugh, J. Absolute bioavailability of clarithromycin after oral administration in humans. Antimicrob. Agents Chemother. 36, 1147–50 (1992).

Chu 1993 Chu, S. et al. Single- and multiple-dose pharmacokinetics of clarithromycin, a new macrolide antimicrobial. J. Clin. Pharmacol. 33, 719–26 (1993).

Chu 1993a Chu, S.Y. et al. Effect of moderate or severe hepatic impairment on clarithromycin pharmacokinetics. J. Clin. Pharmacol. 33, 480–5 (1993).

Davey 1991 Davey, P.G. The pharmacokinetics of clarithromycin and its 14-OH metabolite. J. Hosp. Infect. 19 Suppl A, 29–37 (1991).

Eberl 2007 Eberl, S. et al. Role of p-glycoprotein inhibition for drug interactions: evidence from in vitro and pharmacoepidemiological studies. Clin. Pharmacokinet. 46, 1039–49 (2007).

Hanke 2018 Hanke, N. et al. PBPK Models for CYP3A4 and P-gp DDI Prediction: A Modeling Network of Rifampicin, Itraconazole, Clarithromycin,Midazolam, Alfentanil, and Digoxin. CPT Pharmacometrics Syst. Pharmacol. 7, 647-659 (2018)

Ito 2003 Ito, K., Ogihara, K., Kanamitsu, S.-I. & Itoh, T. Prediction of the in vivo interaction between midazolam and macrolides based on in vitro studies using human liver microsomes. Drug Metab. Dispos. 31, 945–54 (2003).

Jones 2007 Jones, D.R., Ekins, S., Li, L. & Hall, S.D. Computational approaches that predict metabolic intermediate complex formation with CYP3A4 (+b5). Drug Metab. Dispos. 35, 1466–75 (2007).

Kees 1995 Kees, F., Wellenhofer, M. & Grobecker, H. Serum and cellular pharmacokinetics of clarithromycin 500 mg q.d. and 250 mg b.i.d. in volunteers. Infection 23, 168–72 (1995).

Kuepfer 2016 Kuepfer L, Niederalt C, Wendl T, Schlender JF, Willmann S, Lippert J, Block M, Eissing T, Teutonico D. Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model.CPT Pharmacometrics Syst Pharmacol. 2016 Oct;5(10):516-531. doi: 10.1002/psp4.12134. Epub 2016 Oct 19.

Lappin 2011 Lappin, G. et al. Comparative pharmacokinetics between a microdose and therapeutic dose for clarithromycin, sumatriptan, propafenone, paracetamol (acetaminophen), and phenobarbital in human volunteers. Eur. J. Pharm. Sci. 43, 141–50 (2011).

Mayhew 2000 Mayhew, B.S., Jones, D.R. & Hall, S.D. An in vitro model for predicting in vivo inhibition of cytochrome P450 3A4 by metabolic intermediate complex formation. Drug Metab. Dispos. 28, 1031–7 (2000).

McFarland 1997 McFarland, J.W. et al. Quantitative structure-activity relationships among macrolide antibacterial agents: in vitro and in vivo potency against Pasteurella multocida. J. Med. Chem. 40, 1340–6 (1997).

Moj 2017 Moj, D. et al. Clarithromycin, midazolam, and digoxin: application of PBPK modeling to gain new insights into drug-drug interactions and co-medication regimens. AAPS J. 19, 298–312 (2017).

Noreddin 2002 Noreddin, A.M. et al. Pharmacodynamic modeling of clarithromycin against macrolide-resistant [PCR-positive mef(A) or erm(B)] Streptococcus pneumoniae simulating clinically achievable serum and epithelial lining fluid free-drug concentrations. Antimicrob. Agents Chemother. 46, 4029–34 (2002).

PK-Sim Ontogeny Database Version 7.3 (https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/38cf71b384cfc25cfa0ce4d2f3addfd32757e13b/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf)

Polasek 2006 Polasek, T.M. & Miners, J.O. Quantitative prediction of macrolide drug-drug interaction potential from in vitro studies using testosterone as the human cytochrome P4503A substrate. Eur. J. Clin. Pharmacol. 62, 203–8 (2006).

Rengelshausen 2003 Rengelshausen, J. et al. Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin-clarithromycin interaction. Br. J. Clin. Pharmacol. 56, 32–8 (2003).

Rodrigues 1997 Rodrigues, A.D., Roberts, E.M., Mulford, D.J., Yao, Y. & Ouellet, D. Oxidative metabolism of clarithromycin in the presence of human liver microsomes. Major role for the cytochrome P4503A (CYP3A) subfamily. Drug Metab. Dispos. 25, 623–30 (1997).

Rodvold 1999 Rodvold, K.A. Clinical pharmacokinetics of clarithromycin. Clin. Pharmacokinet. 37, 385–98 (1999).

Salem 2003 Salem, I.I. & Düzgünes, N. Efficacies of cyclodextrin-complexed and liposome-encapsulated clarithromycin against Mycobacterium avium complex infection in human macrophages. Int. J. Pharm. 250, 403–14 (2003).

Schlender 2016 Schlender JF, Meyer M, Thelen K, Krauss M, Willmann S, Eissing T, Jaehde U. Development of a Whole-Body Physiologically Based Pharmacokinetic Approach to Assess the Pharmacokinetics of Drugs in Elderly Individuals. Clin Pharmacokinet. 2016 Dec;55(12):1573-1589.

Seithel 2007 Seithel, A. et al. The influence of macrolide antibiotics on the uptake of organic anions and drugs mediated by OATP1B1 and OATP1B3. Drug Metab. Dispos. 35, 779–86 (2007).