Building and Evaluation of a PBPK Model for Clarithromycin in Adults

Version	0.1
OSP Version	8.0
Author	

Table of Contents

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.

Objectives were to develop a fully mechanistic PBPK model for clarithromycin, describing its metabolism by CYP3A4 and its mechanism-based inactivation of the respective enzyme as well as its inhibition of P-gp.

The presented Clarithromycin model was developed by Moj et al. (Moj 2017) and revised by Hanke et al. (Hanke 2018) and is publically available on GitHub (...).

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.

A typical European individual was used for the development of the clarithromycin model. The relativ tissue specific expression of CYP3A4 was implemented in accordance with literature using the PK-Sim expression database RT-PCR profile. Enterohepatic cycling was enabled as it is active under physiological conditions.

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

The model was then verified by simulating:

- the whole reported dose range including single and multiple doses
- DDIs with CYP3A4 or P-gp substrates (shown elsewhere)

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 clarithromycin. 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
				Renal plasma

Parameter	Unit	Value	Source	Description
CLren	mL/min	110-213	Rodvold 1999	Renal plasma clearance
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. The clarithromycin model was developed using 17 clinical studies, covering a dosing range from 100 to 1200 mg.

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 (test data):

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
Abduljialil 2009	Oral administration of 500 mg twice a day for 3.5 days

2.3 Model Parameters and Assumptions

2.3.1 Absorption

The specific intestinal permeability was optimized during parameter identification to accurately describe the absorption of clarithromycin after oral administration.

2.3.2 Distribution

Values for logP and fu were fixed according to literature values.

For clarithromycin, it was not possible to adequately describe the concentration-time profile after intravenous administration using standard input parameters (e.g. logP) and calculation methods. Simulated concentration-time profiles over-predicted Cmax and under-predicted the observed data for time > Tmax. According to literature, clarithromycin accumulates in mononuclear and polymorphonuclear leukocytes, probably via active transport (Ishiguro 1989). This process was implemented, and it improved the model significantly. Due to limited knowledge on this transport, an adjustment of the clarithromycin permeability between plasma and RBC compartments was applied.

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

The final model applies partitioning into blood cells, metabolism by CYP3A4 including mechanism-based auto-inactivation and a renal clearance.

Metabolism was described using Michaelis Menten kinetics, while the Michaelis-Menten constant Km was taken from in-vitro experiments from literature and the turnover rate kcat was optimized during parameter identification.

Ki and kinact to describe the mechanism-based inhibition of CYP3A4 were optimized during parameter identification.

A kidney plasma clearance was implemented to describe the renal elimination of clarithromycin. The specific renal clearance CLren was optimized during parameter identification.

2.3.4 Automated Parameter Identification

This is the result of the final parameter identification.

Model Parameter	Optimized Value	Unit
`CYP3A4 kcat`	76.5	1/min
`CLren`	100	mL/min
`Specific intestinal permeability`	1.23 E-6	dm/min
`Perm. into blood cells`	3.62 E-5	dm/min
`Perm. out of blood cells`	1.04 E-6	dm/min

3 Results and Discussion

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

The model was evaluated covering data from studies including in particular

- intravenous and oral administrations

- a dose range of 100 mg to 1200 mg
- single and multiple doses

The model quantifies metabolism via CYP3A4, including also the mechanism-based inhibition of the respective enzyme, as well as elimination via kidney.

The model also includes inhibition of p-gp (shown elsewhere).

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	Publication-Salem 2003	Measurement	True	
Reference pH	2.4	Publication-Salem 2003	Measurement	True	
Lipophilicity	2.3 Log Units	Publication-Lappin 2011	Measurement	True	
Fraction unbound (plasma, reference value)	0.299	Publication-Chu 1993	Measurement	True	
Specific intestinal permeability (transcellular)	1.23E-06 dm/min	Parameter Identification-optimized	fit	True	
Is small molecule	Yes				
Molecular weight	747.9534 g/mol				

Name	Value	Value Origin	Alternative	Default	
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	Publication-Rodrigues 1997	
kcat	76.5 1/min	Parameter Identification	

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	Publication-Eberl 2007	

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	Publication-Vermeer 2016	

Inhibition: OATP1B3-Vermeer 2016

Molecule: OATP1B3

Parameters

Name	Value	Value Origin	
Ki	14 µmol/l	Publication-Vermeer 2016	

Formulation: Tablet Clarithromycin

Type: Weibull

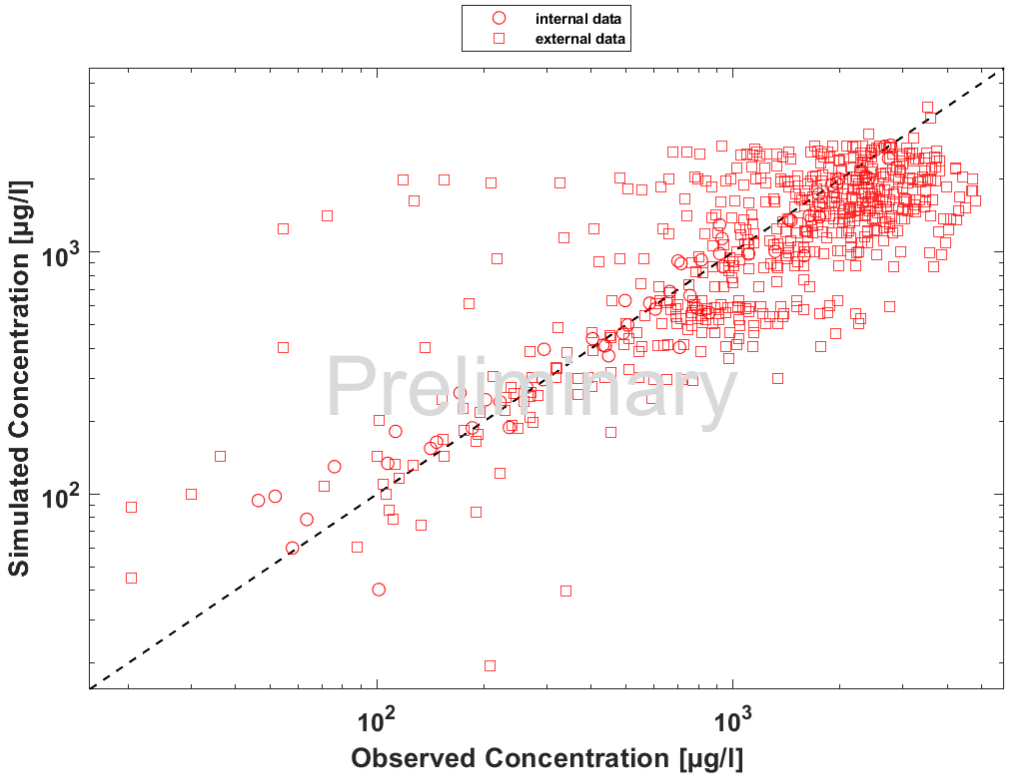
Parameters

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

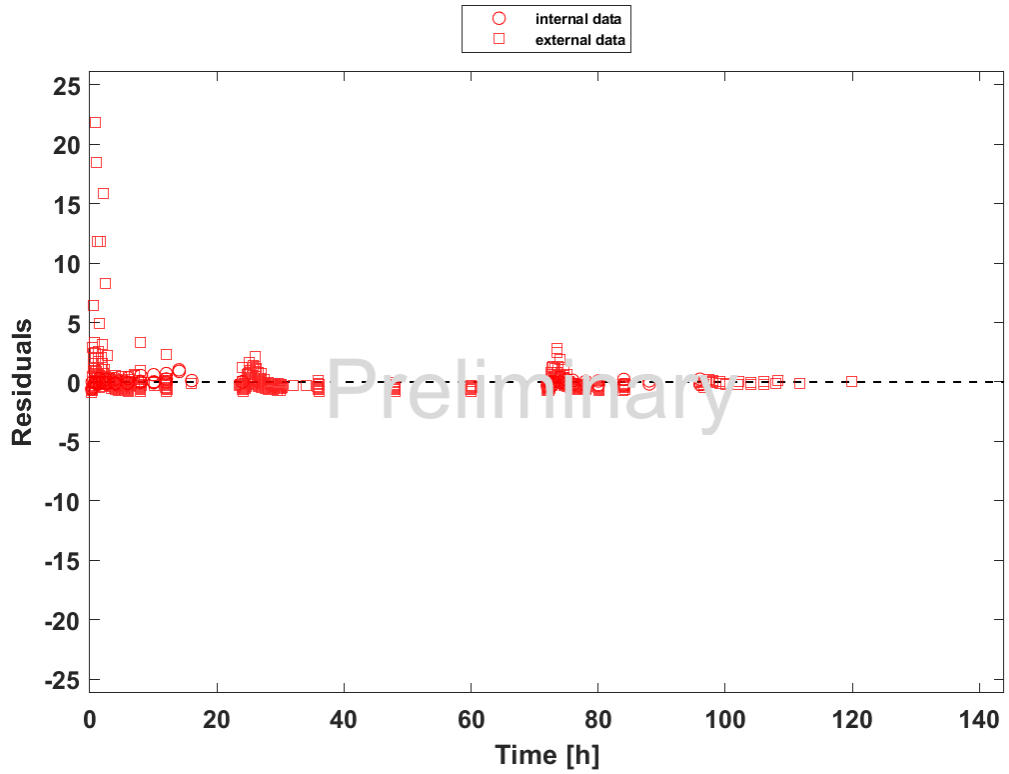
3.2 Diagnostics Plots

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



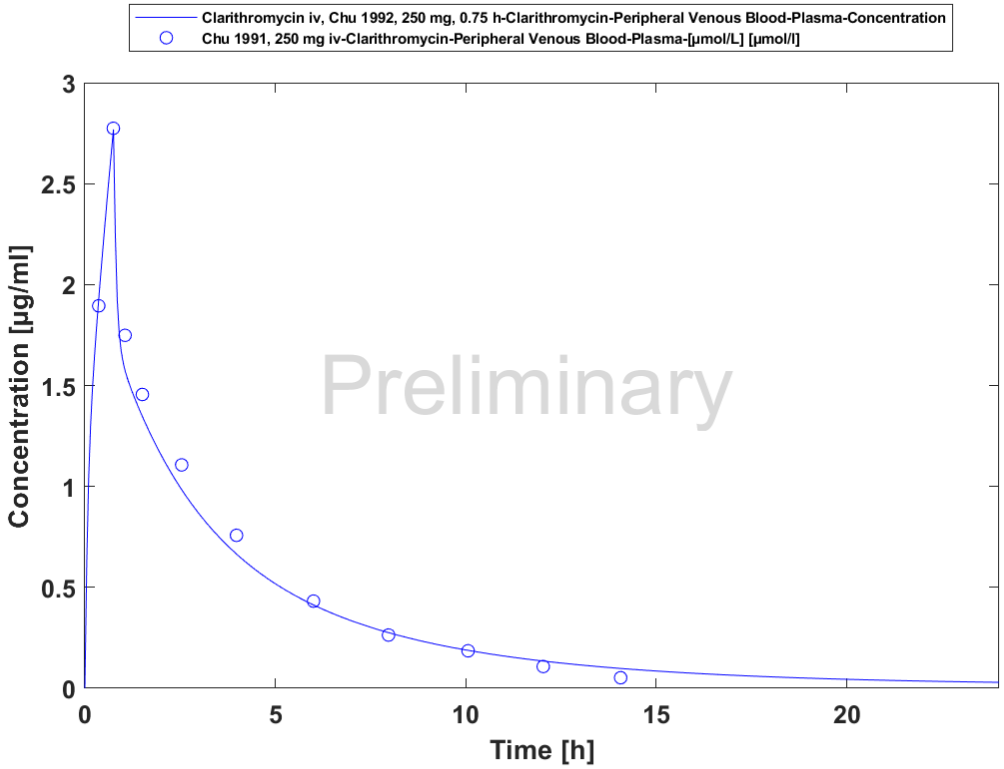
Goodness of fit plor for concentration in plasma

GMFE = 1.575193

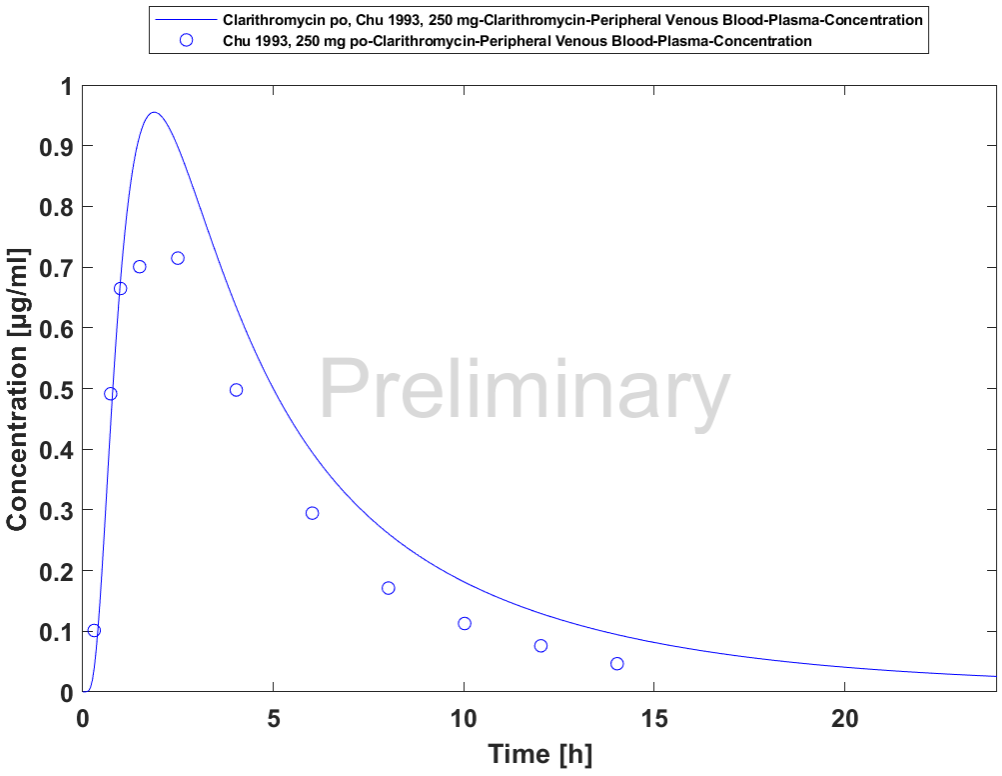
3.3 Concentration-Time Profiles

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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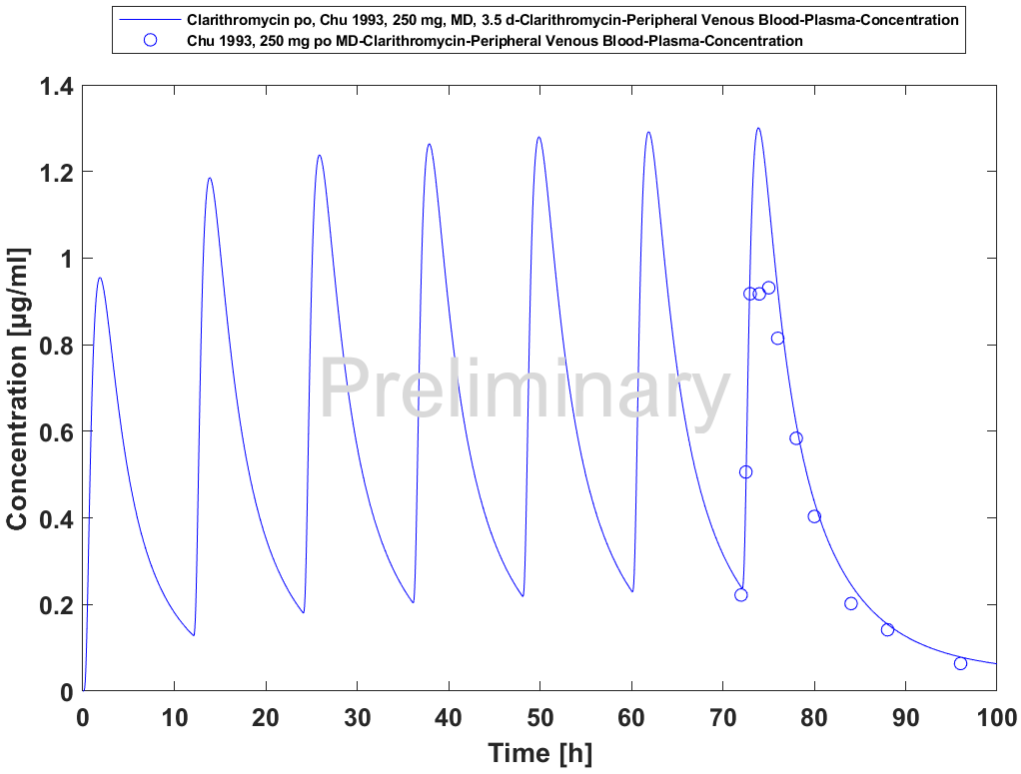

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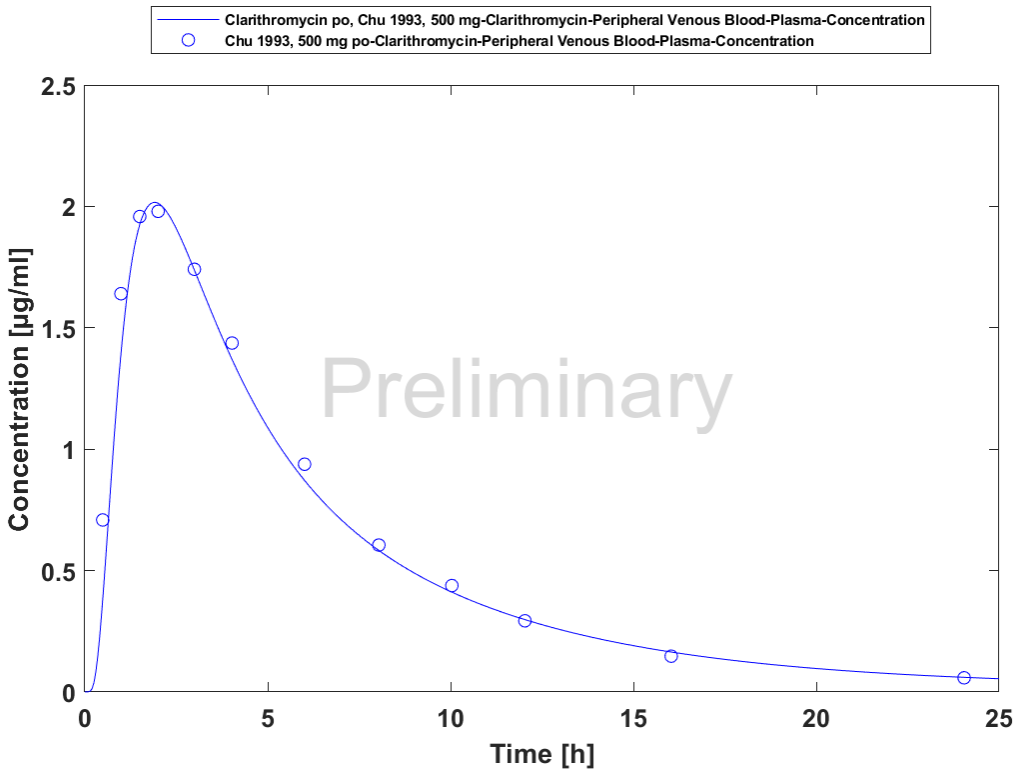

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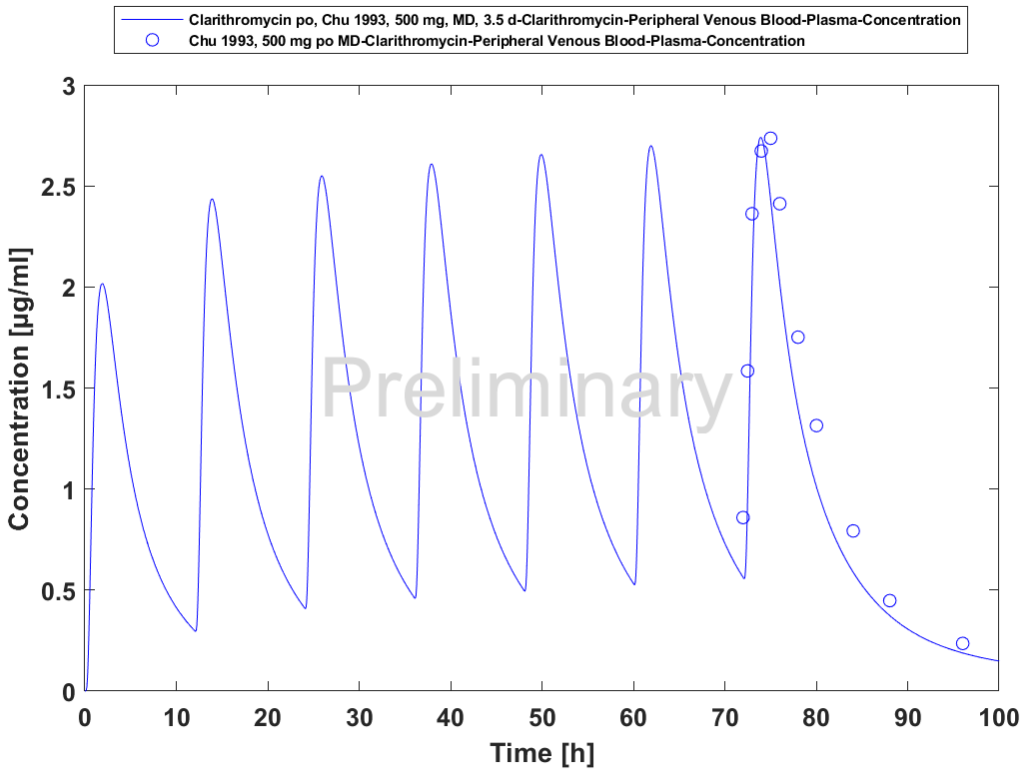
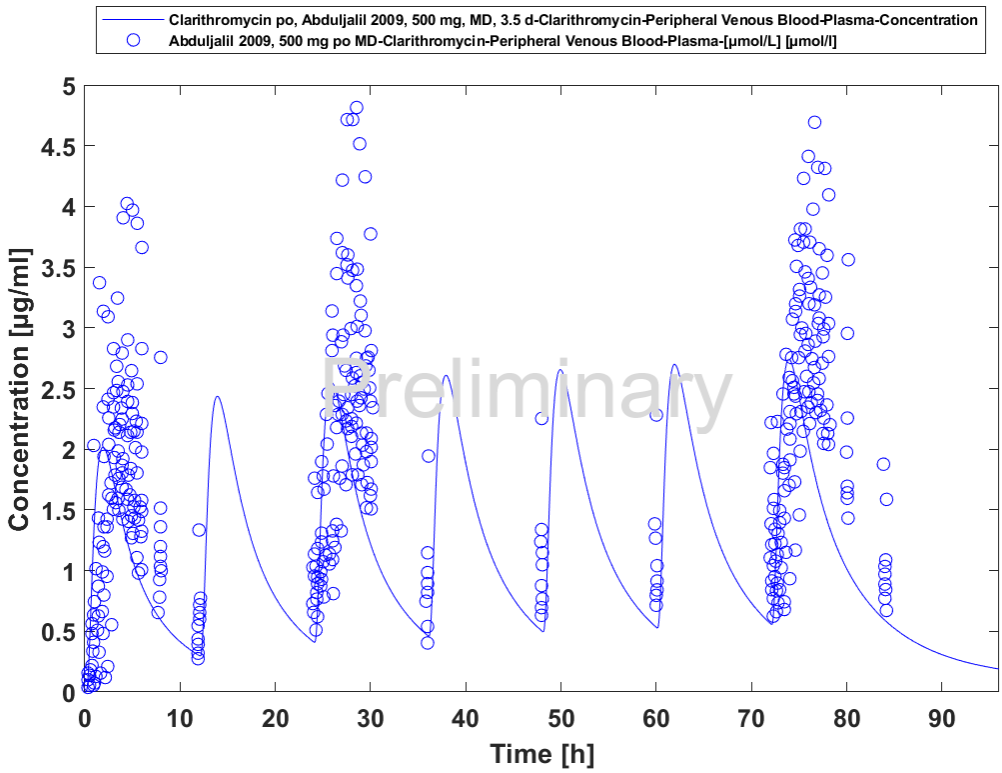


Time Profile Analysis

3.3.2 Model Verification



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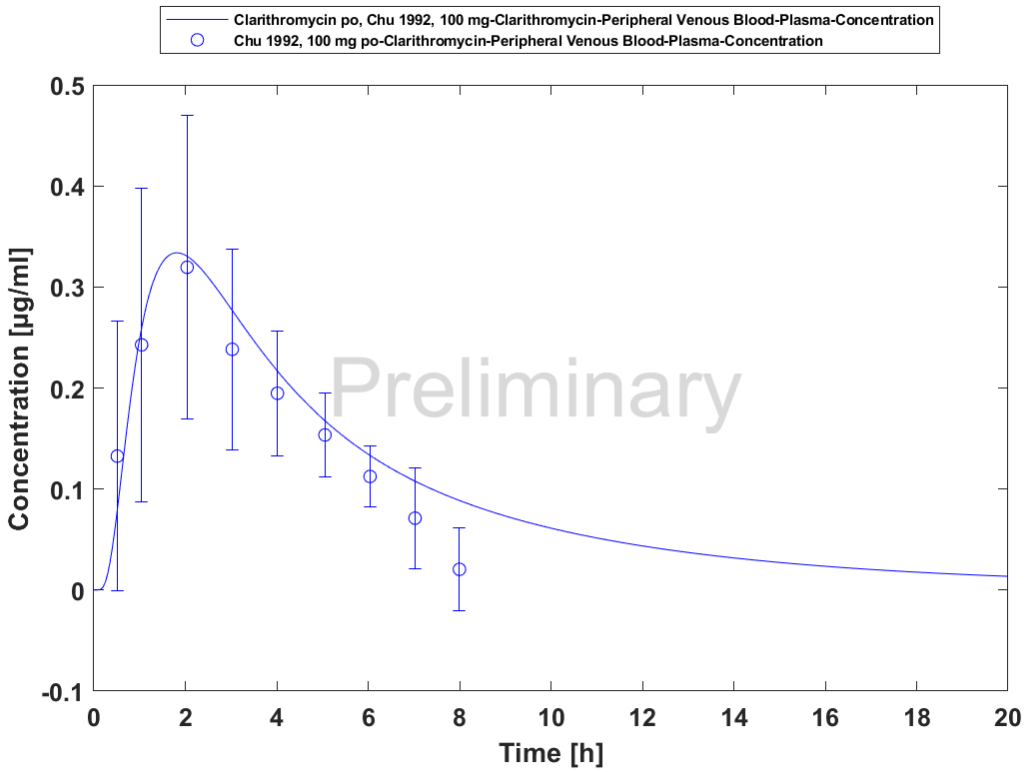

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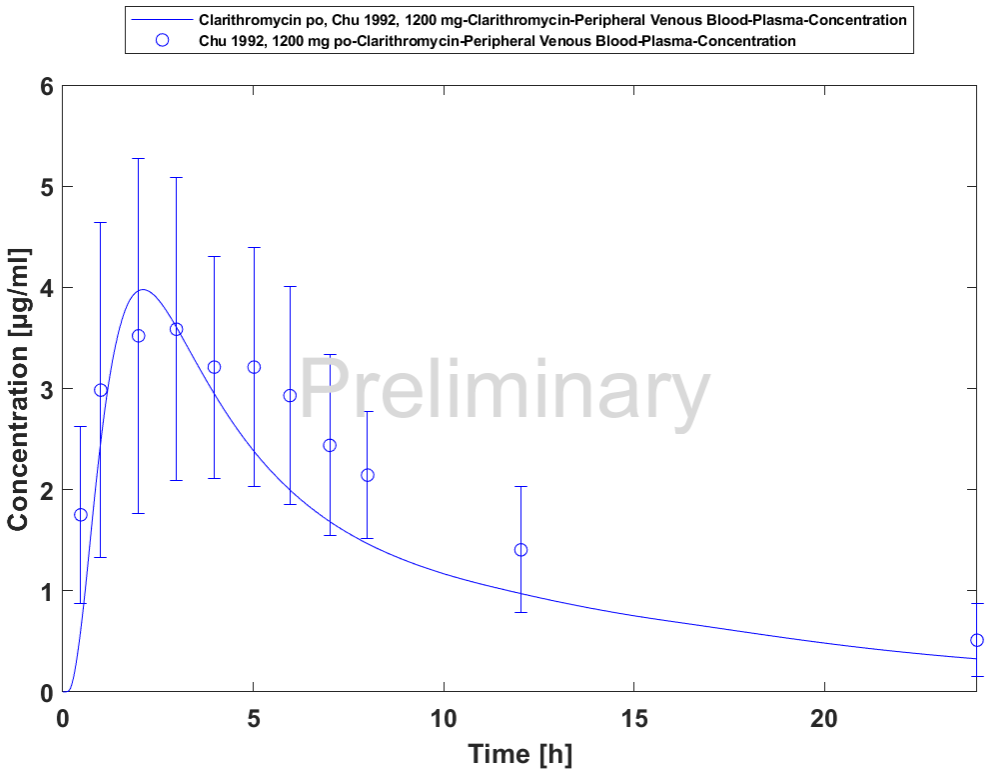

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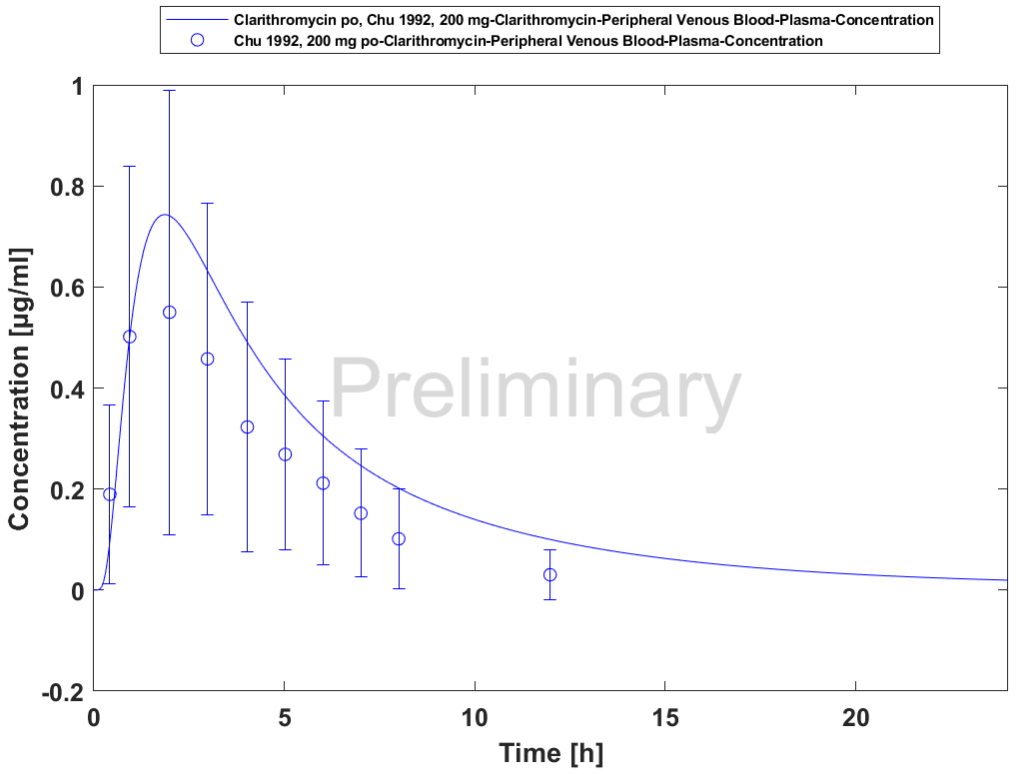

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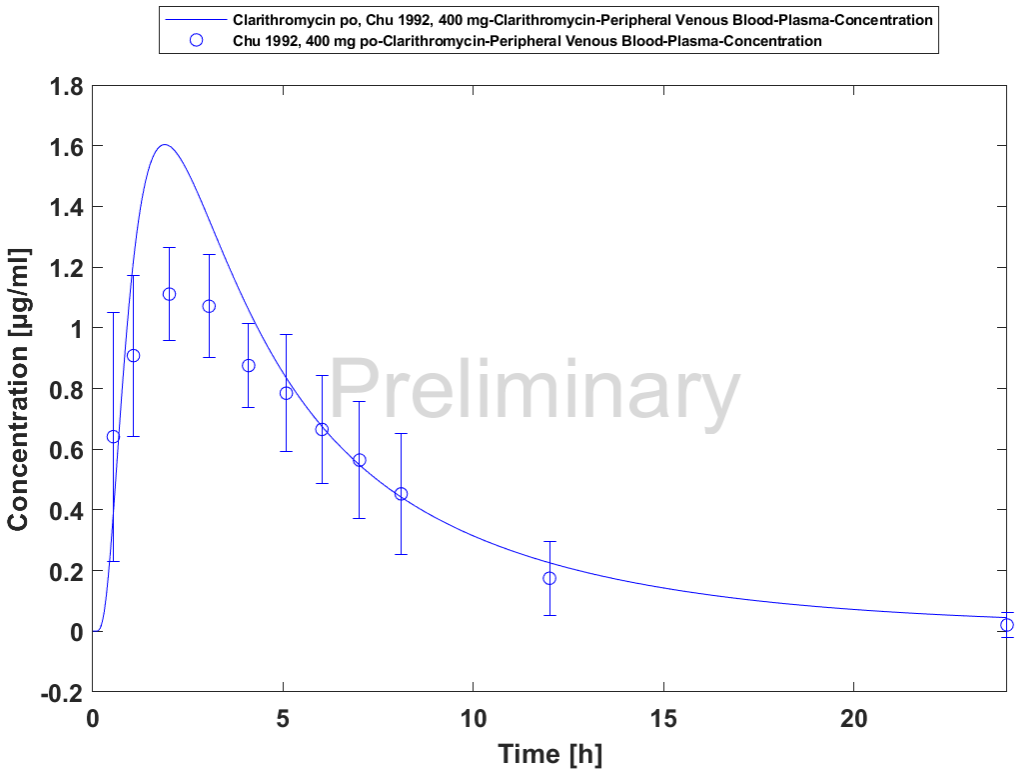

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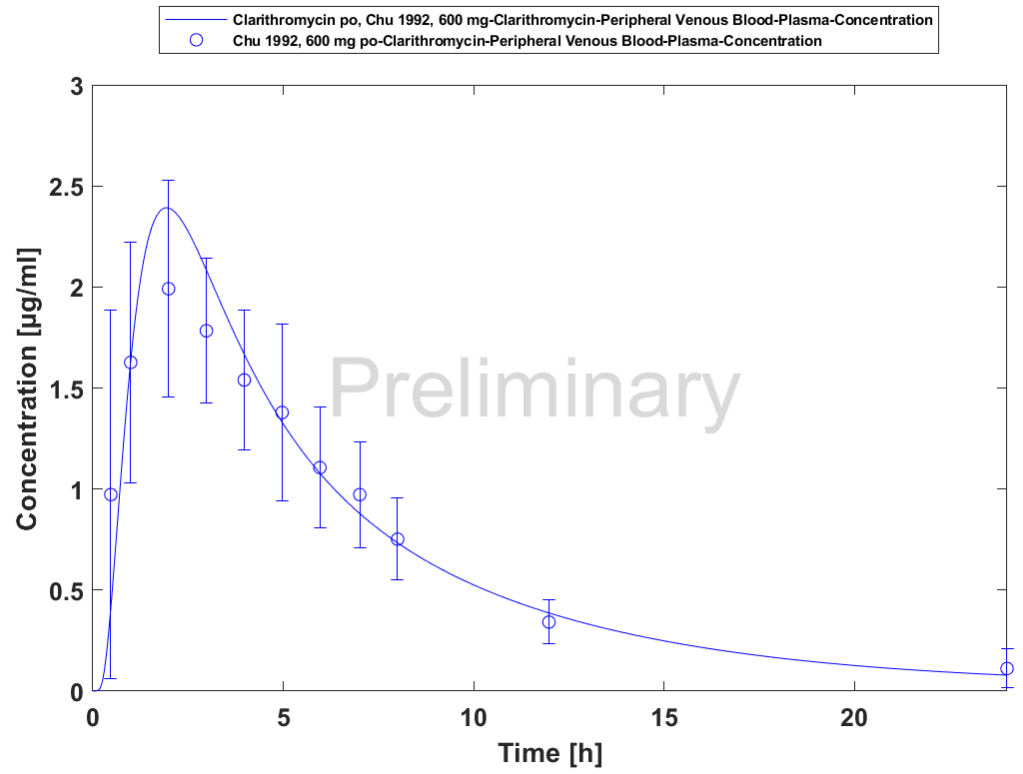

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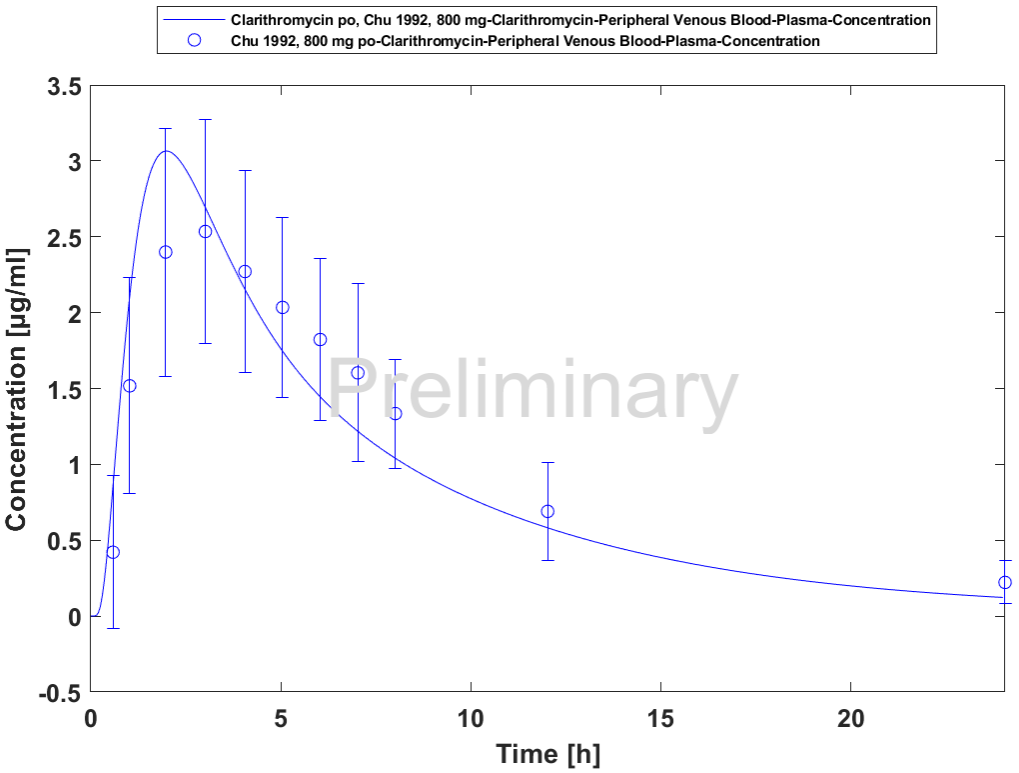

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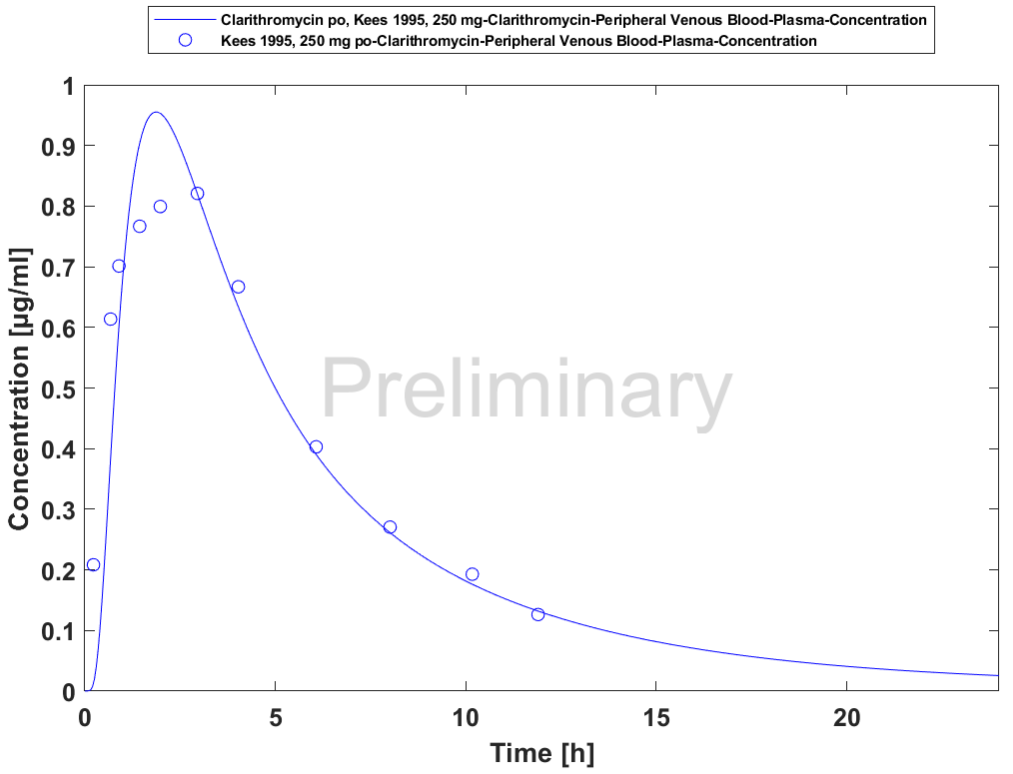

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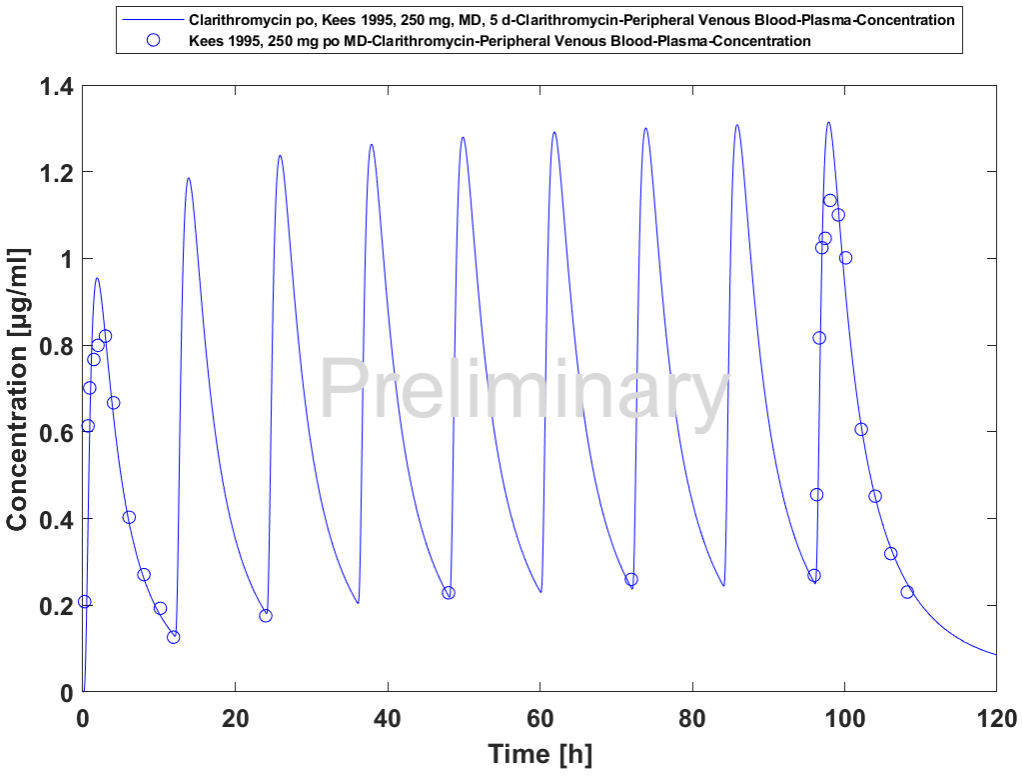

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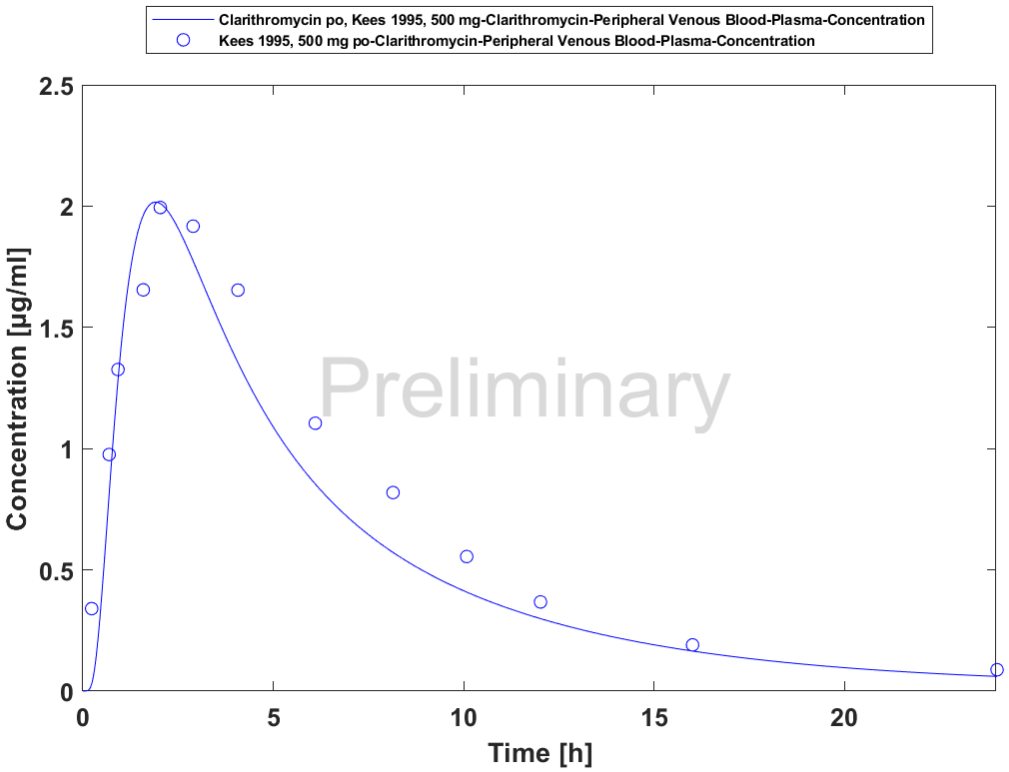

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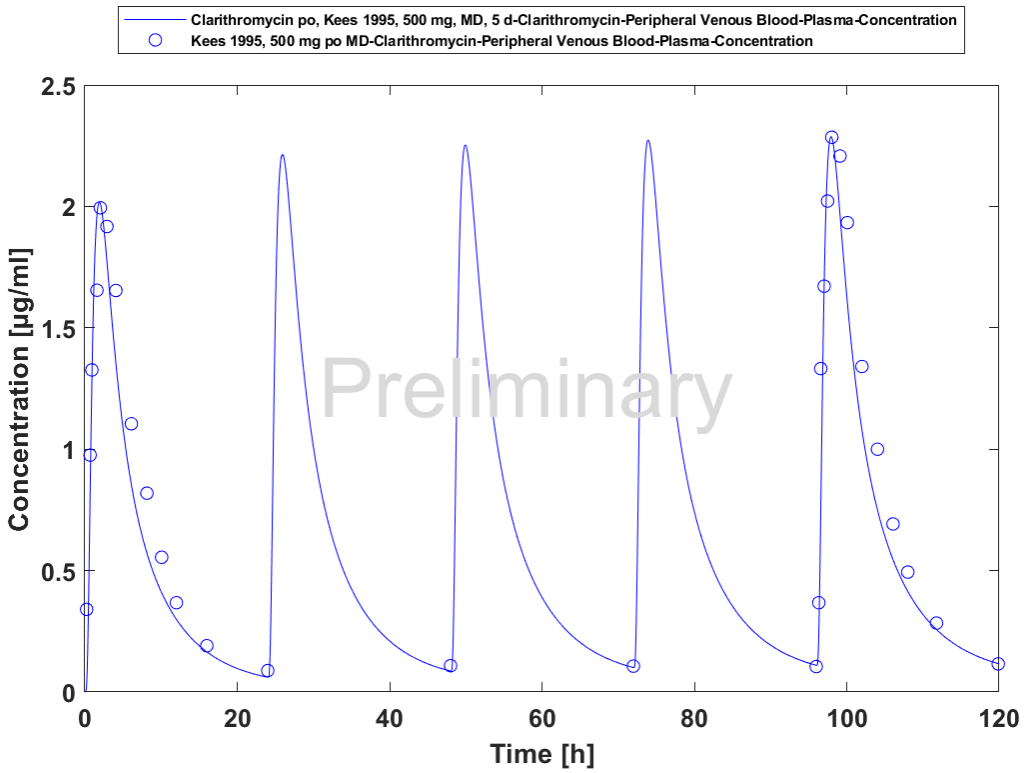

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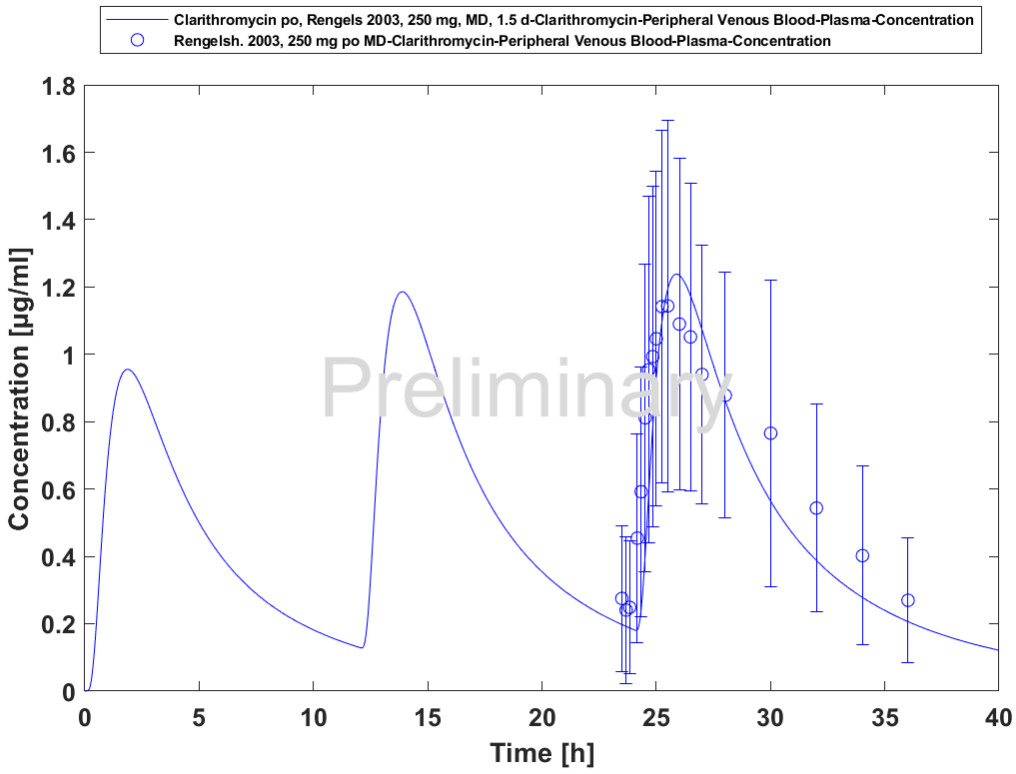

Time Profile Analysis

4 Conclusion

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

In particular, it applies quantitative metabolism by CYP3A4 by taking into account the mechanism-based inactivation of CYP3A4 as well as renal elimination of clarithromycin. Thus, the model is fit for purpose to be applied for the investigation of drug-drug interactions with regard to inhibition of CYP3A4 and P-gp.

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