Building and Evaluation of a PBPK Model for Verapamil in Adults

Version	**1.0**
OSP Version	8.0
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Table of Contents

1 Introduction

Verapamil is used for the treatment of high blood pressure, angina (chest pain from not enough blood flow to the heart), and supraventricular tachycardia.

Its major metabolizing enzyme is CYP3A4, but also CY2C8 to some extent (Tracy 1999). The dose- and time-dependent nonlinear behavior of verapamil is well described through implementation of the synergistic CYP3A4 mechanism-based (auto-)inactivation by verapamil.

The presented verapamil model was established using observed concentration-time profiles of more than 10 clinical studies with doses from 0.1 mg to 240 mg in different verapamil dosing schedules including multiple doses over up to 10 days and different routes of administration (intravenous, single and multiple oral administration).

The herein presented model building and evaluation report evaluates the performance of the PBPK model for verapamil in (healthy) adults.

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by e.g. Kuepfer et al. (Kuepfer 2016). The relevant anthropometric (height, weight) and physiological information (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). This information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

Variability of plasma proteins and CYP enzymes are integrated into PK-Sim® and described in the publicly available PK-Sim® Ontogeny Database Version 7.3 (Schlender 2016) or otherwise referenced for the specific process.

First, a base mean model was built and adjusted to clinical data including single and multiple dose studies with oral applications of verapamil to find an appropriate structure to describe the pharmacokinetics in plasma. The mean PBPK model was developed using a typical European individual adjusted to the demography of the respective study population. The relative tissue specific expressions of enzymes predominantly being involved in the metabolism of verapamil were derived from RT-PCR data from Nishimura 2003.

Unknown parameters (see below) were identified using the Parameter Identification module provided in PK-Sim®. Structural model selection was mainly guided by visual inspection of the resulting description of data and biological plausibility.

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 verapamil. The obtained information from literature is summarized in the table below.

Parameter	Unit	Value	Source	Description
MW	g/mol	454.6	https://www.drugbank.ca/	Molecular weight
pK_a	8.92	(base)	Perdaems 2010	Acid dissociation constant
Solubility (pH)	mg/L	46.0	Heikkinen 2012	Water solubility
logP		2.7	Sandström 1999	Partition coefficient between octanol and water
fu		0.1	Vogelpoel 2004	Fraction unbound in plasma
KI	µmol/L	1.2	Rowland-Yeo 2011	Inhibition constant

2.2.2 Clinical Data

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

2.2.2.1 Model Building and parameterizing of CYP3A4 interaction

The following studies were used for model building and parameterization of CYP3A4 interaction:

Publication	Arm / Treatment / Information used for model building
Barbarash 1988	Healthy subjects receiving single intravenous doses of 10 mg and single oral doses of 120 mg
Johnston 1981	Healthy subjects receiving single intravenous doses of 0.1 mg/kg and single oral doses of 120 mg
McAllister 1982	Healthy subjects receiving single intravenous doses of 10 mg and single oral doses of 120 mg

2.2.2.2 Model verification

The following studies were used for model verification:

Publication	Arm / Treatment / Information used for model building
Freedman 1981	Healthy subjects receiving single intravenous doses of 13.1 mg and single oral doses of 80 mg
Maeda 2011	Healthy subjects receiving single oral doses of 80 mg
Mooy 1985	Healthy subjects receiving single intravenous doses of 3 mg and single oral doses of 80 mg
Streit 2005	Healthy subjects receiving single intravenous doses of 5 mg
Hla 1987	Healthy subjects receiving multiple oral doses of 120 mg BID
Joergenson 1988	Healthy subjects receiving multiple oral doses of 120 mg BID
Shand 1981	Healthy subjects receiving multiple oral doses of 120 mg TID
Johnson 2001	Healthy subjects receiving multiple oral doses of 400 mg verapamil QD. On day 14, subjects receive a single oral verapamil dose of 3 mg.
van Haarst 2009	Healthy subjects receiving multiple oral doses of 180 mg BID
Karim 1995	Healthy subjects receiving single oral doses of 240 mg
Meredith 1985	Healthy subjects receiving single oral doses of 160 mg

2.3 Model Parameters and Assumptions

2.3.1 Absorption

Absorption observed in clinical studies can be fully explained by passive 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, Elimination and Induction

Verapamil is metabolized by CYP3A4 and CYP2C8.

Mechanism-based inactivation of CYP3A4 (Rowland-Yeo 2011) was taken into account.

2.3.4 Automated Parameter Identification

The parameter identification tool in PK-Sim has been used to estimate selected model parameters by adjusting to PK data of the clinical studies that were used in the model building process.

The is result of the final parameter identification is shown in the table below:

Model Parameter	Optimized Value	Unit
Specific intestinal permeability	1.6341738226E-05	cm/min
Solubility at reference pH	43514.8753161441	mg/l
kinact CYP3A4	0.0376212371	1/min
mucosa permeability	0.0015095540335	cm/min

3 Results and Discussion

The PBPK model for verapamil was developed and evaluated using publically available, clinical pharmacokinetic data from studies listed in Section 2.2.2.

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.

Formulation: controlled release

Type: Weibull

Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	38.5979819554 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-11-26 13:43	
Lag time	0 min		
Dissolution shape	1.2441115042	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-11-26 13:43	
Use as suspension	Yes		

Formulation: solution

Type: Dissolved

Compound: Verapamil

Parameters

Name	Value	Value Origin	Alternative	Default	
Solubility at reference pH	43514.8753161441 mg/l	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 2' on 2019-11-26 10:33	Measurement	True	
Reference pH	6.54		Measurement	True	
Lipophilicity	2.7 Log Units		Measurement	True	
Fraction unbound (plasma, reference value)	0.1		Measurement	True	
Specific intestinal permeability (transcellular)	1.6341738226E-05 cm/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 2' on 2019-11-26 10:33	fitted	True	
Is small molecule	Yes				
Molecular weight	454.6 g/mol				
Plasma protein binding partner	Albumin				

Calculation methods

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

Processes

Metabolizing Enzyme: CYP2C8-Tracy 1999

Molecule: CYP2C8

Parameters

Name	Value	Value Origin	
In vitro CL/recombinant enzyme	0.057 µl/min/pmol rec. enzyme		
CLspec/[Enzyme]	0.3179498362 l/µmol/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 1' on 2019-11-26 09:16	

Metabolizing Enzyme: CYP3A4-Tracy 1999

Molecule: CYP3A4

Parameters

Name	Value	Value Origin	
In vitro CL/recombinant enzyme	0.8333 µl/min/pmol rec. enzyme		
CLspec/[Enzyme]	4.6482034823 l/µmol/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 1' on 2019-11-26 09:16	

Inhibition: CYP3A4-Rowland-Yeo 2010

Molecule: CYP3A4

Parameters

Name	Value	Value Origin	
kinact	0.0376212371 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 2' on 2019-11-26 10:33	
K_kinact_half	1.2 µmol/l		

Systemic Process: Glomerular Filtration-GFR

Species: Human

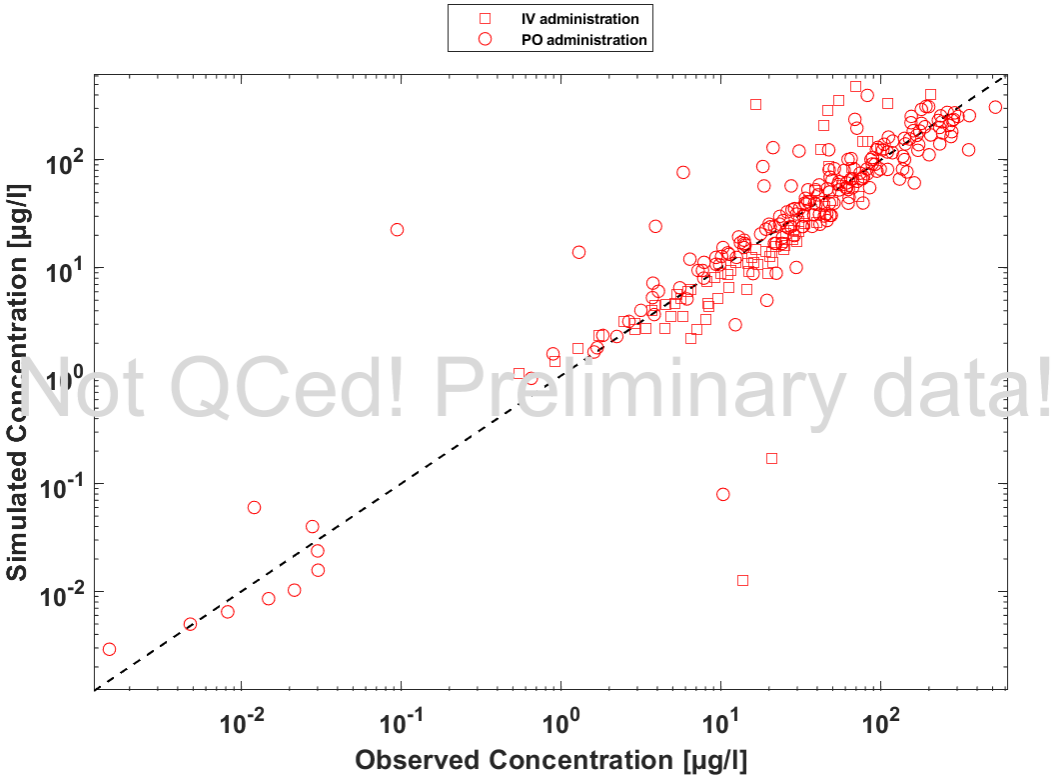
Parameters

Name	Value	Value Origin	
GFR fraction	1		

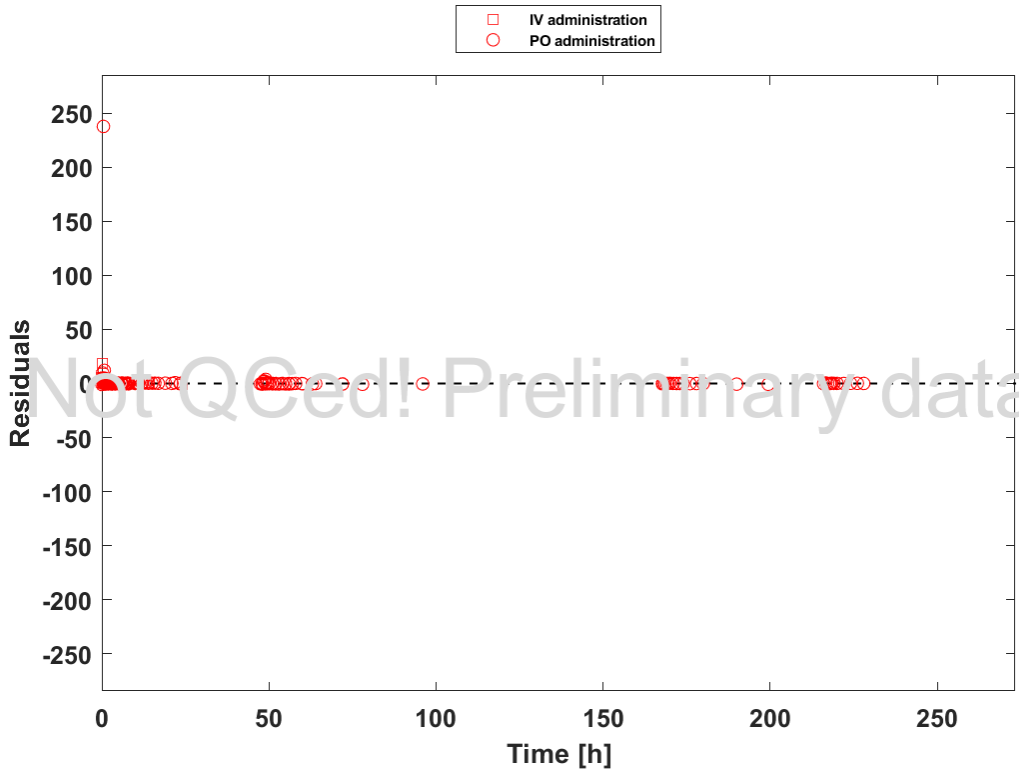
3.2 Diagnostics Plots

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



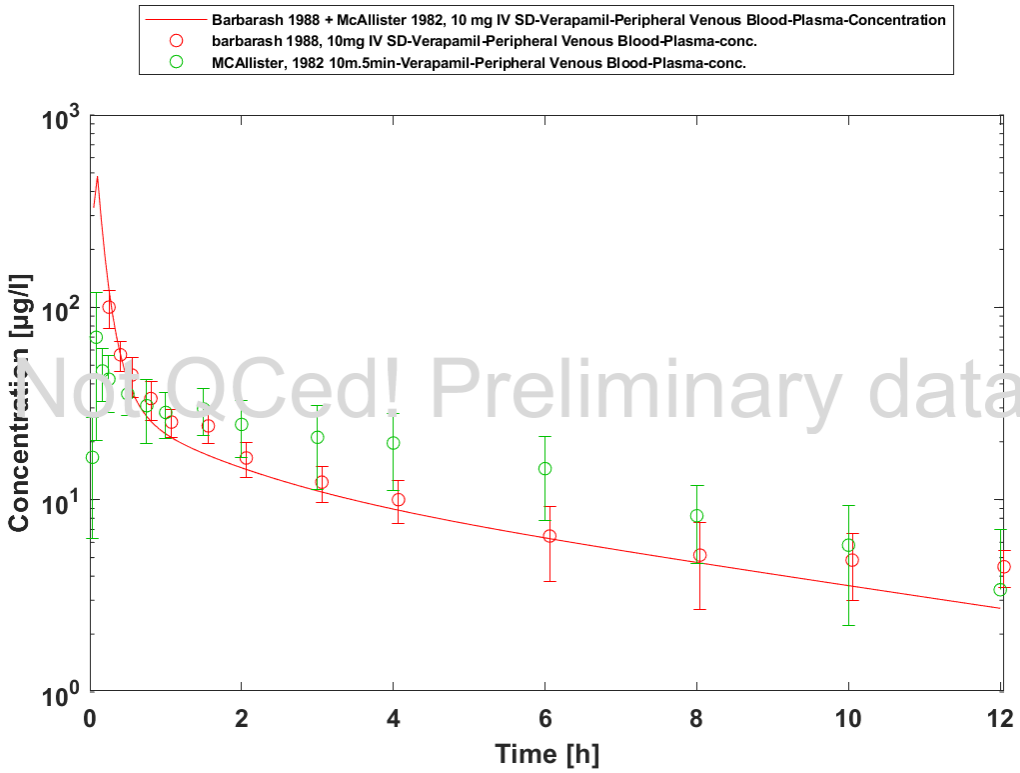
Goodness of fit plor for concentration in plasma

GMFE = 1.602124

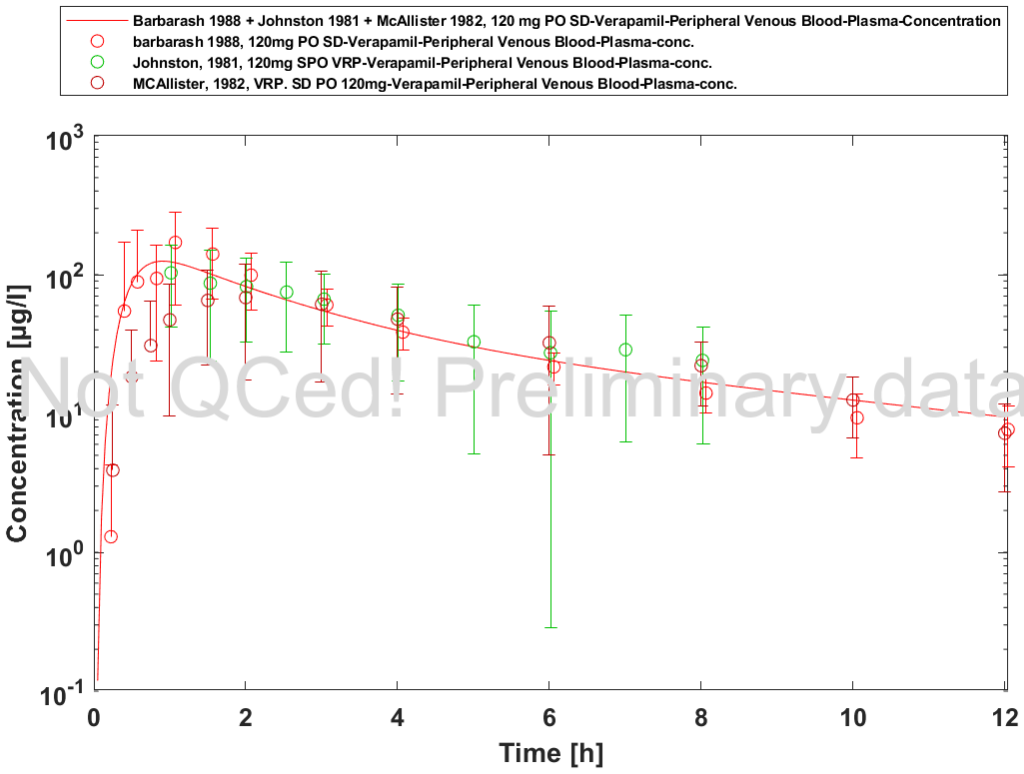
3.3: Concentration-Time Profiles

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

3.3.1 Model Building

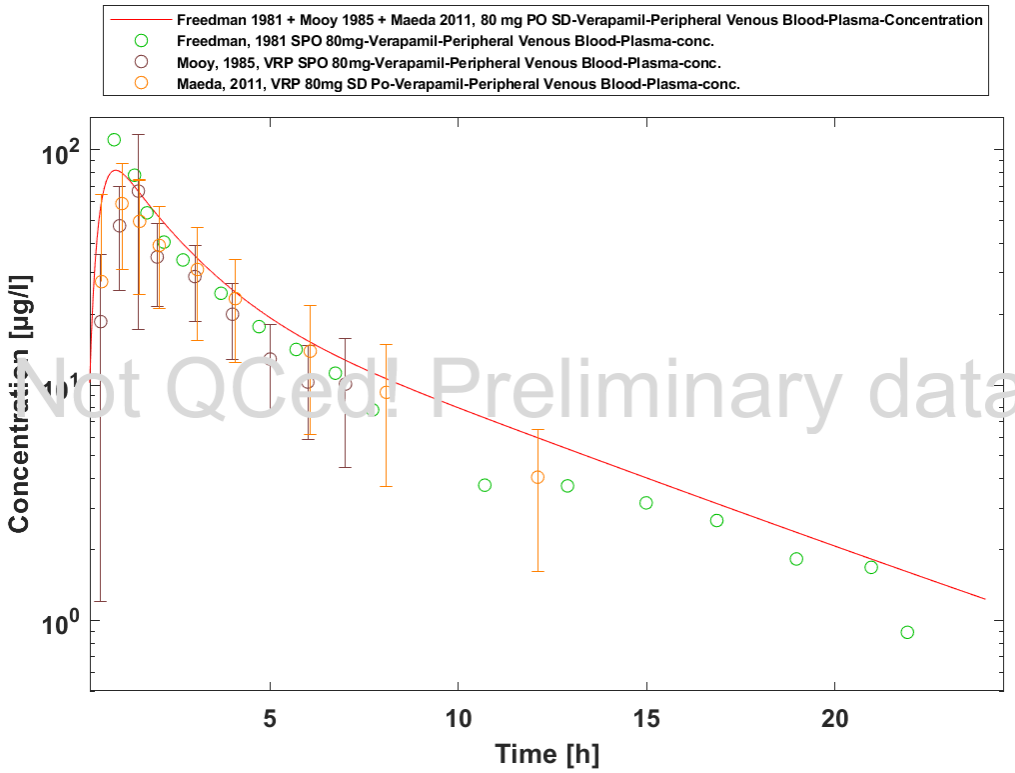


Time Profile Analysis



Time Profile Analysis

3.3.2 Model verification



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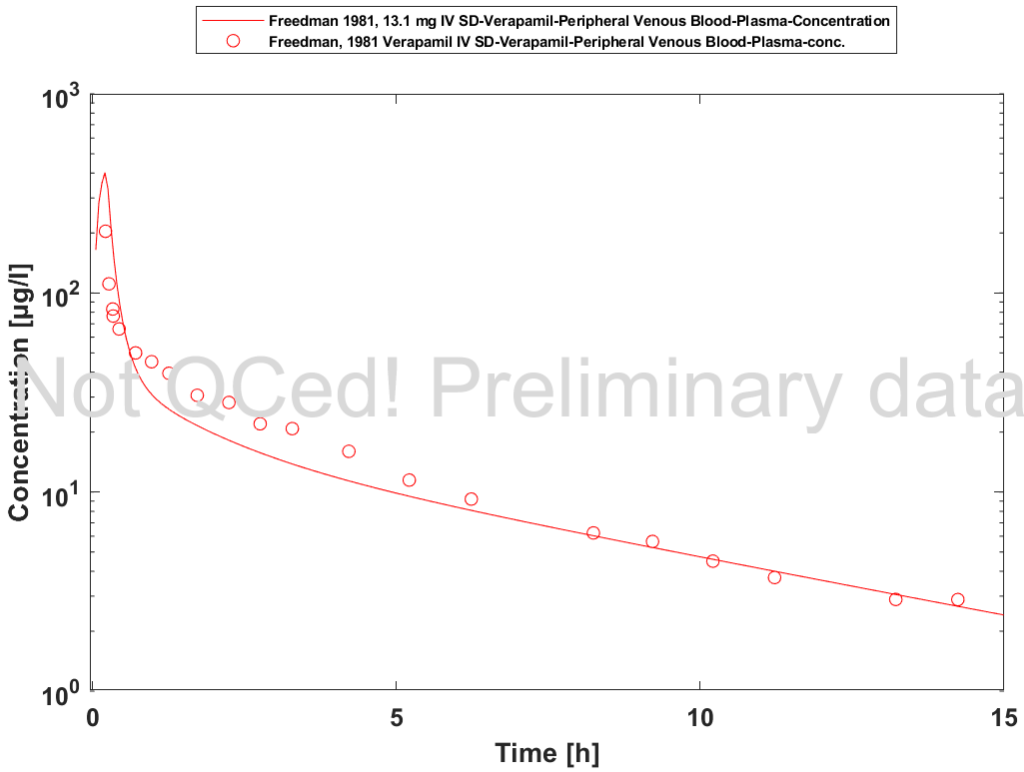

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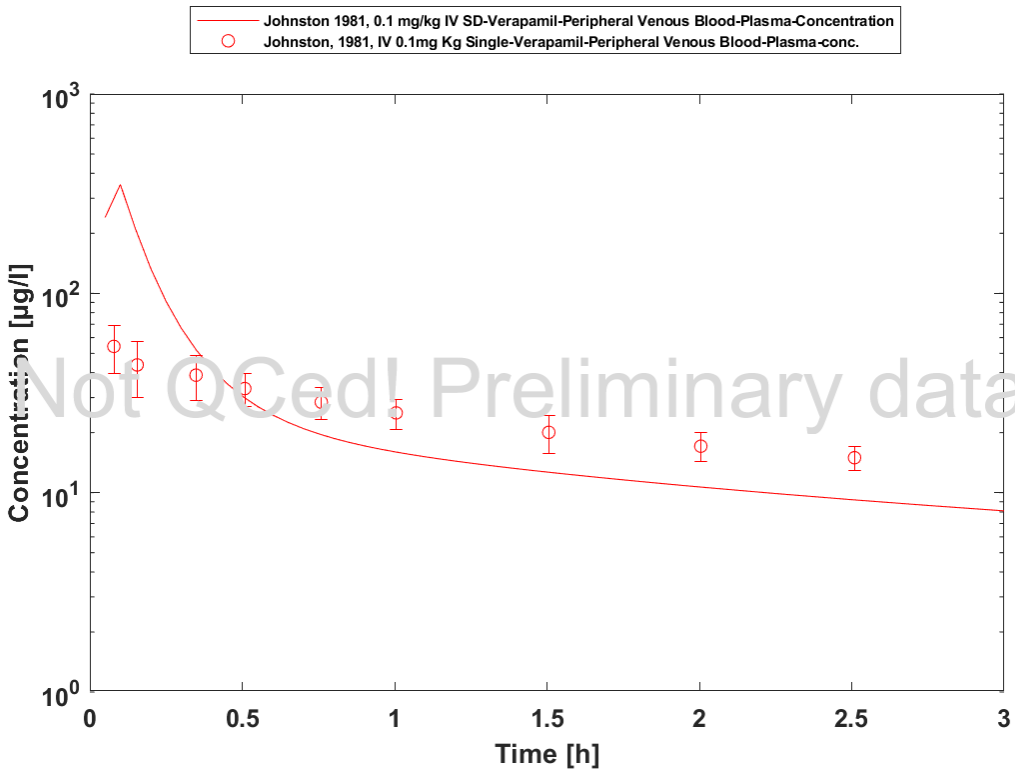

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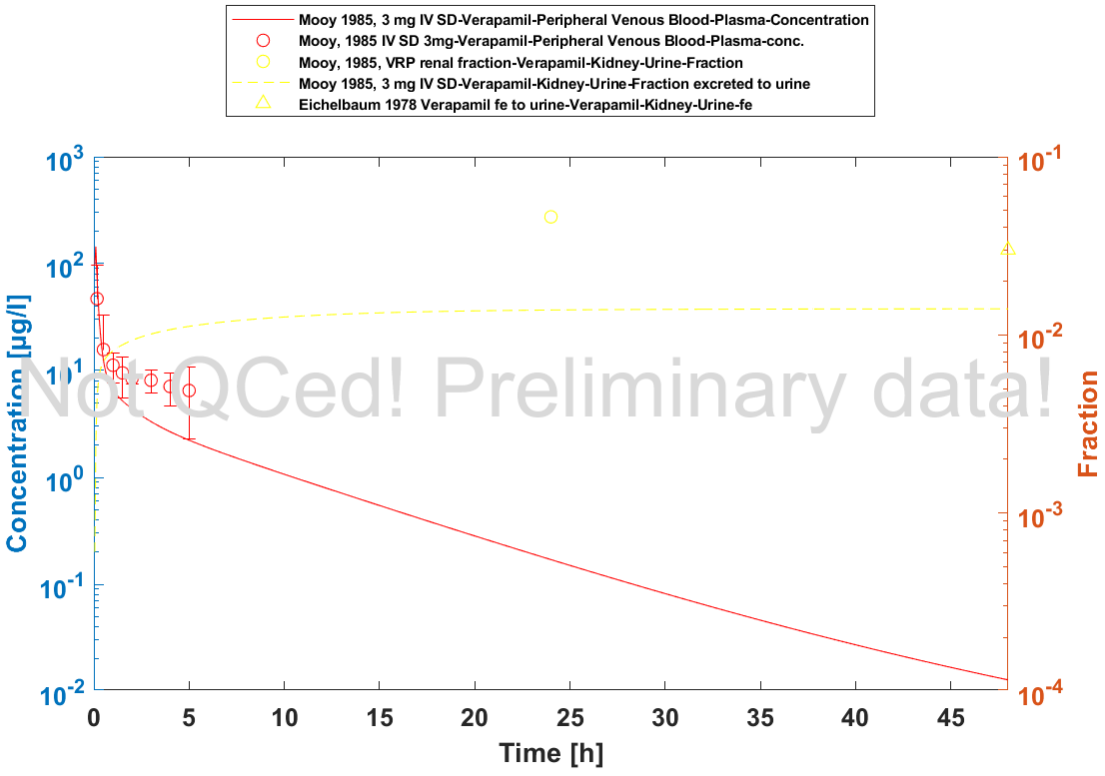

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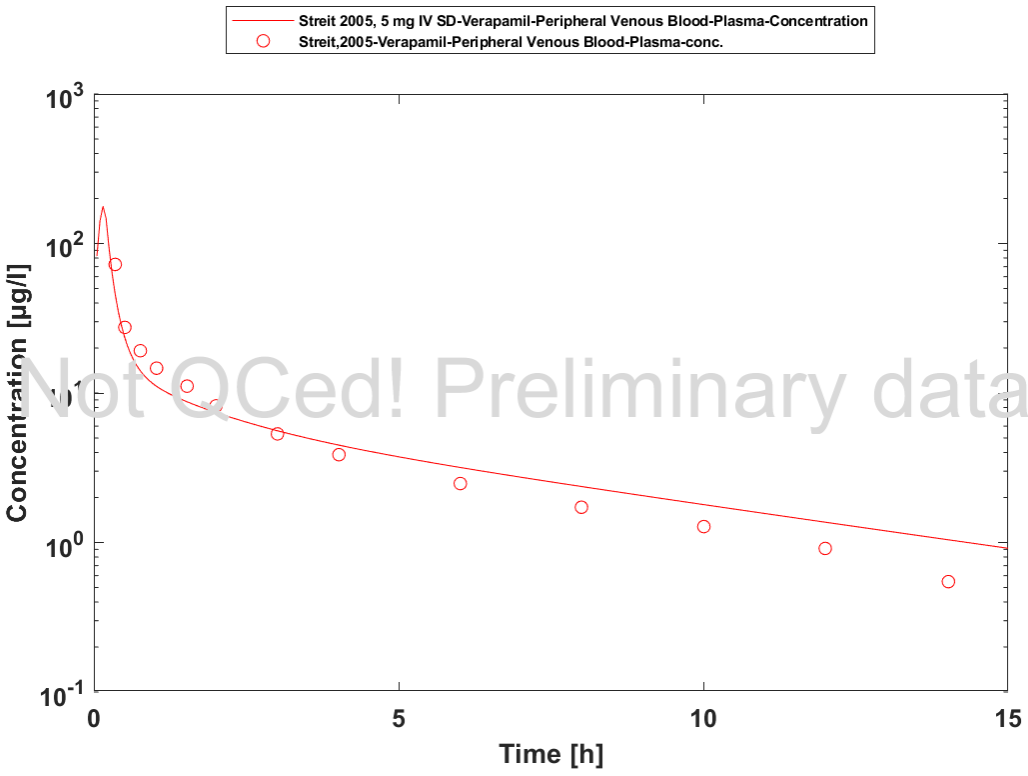

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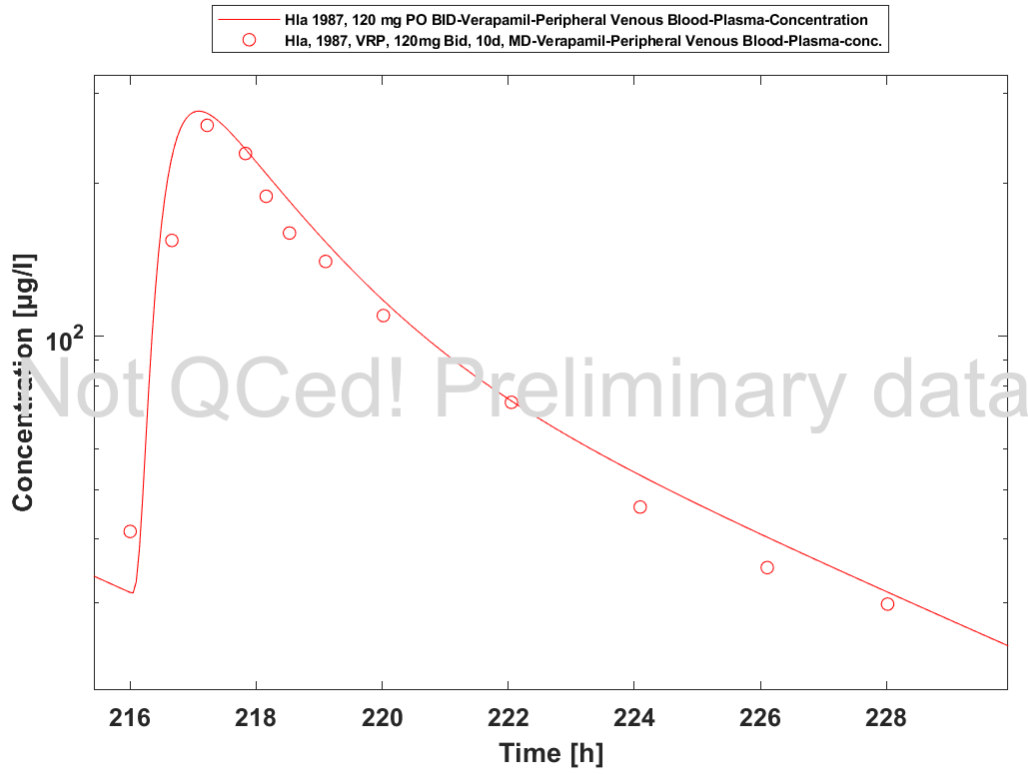

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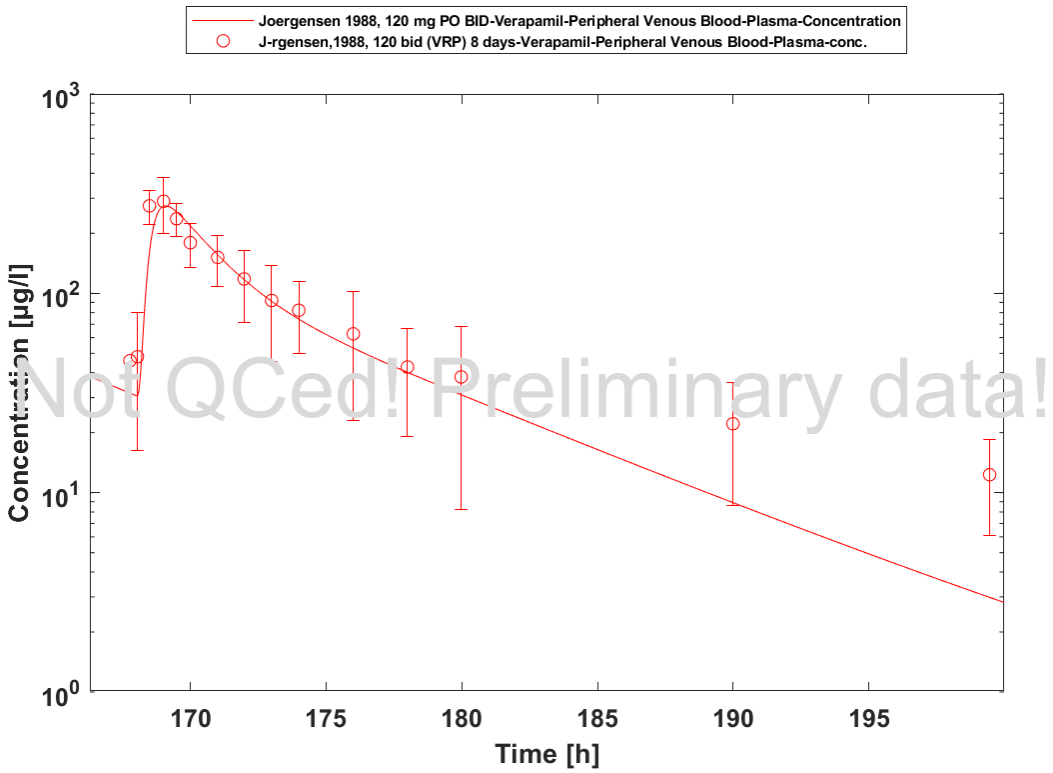

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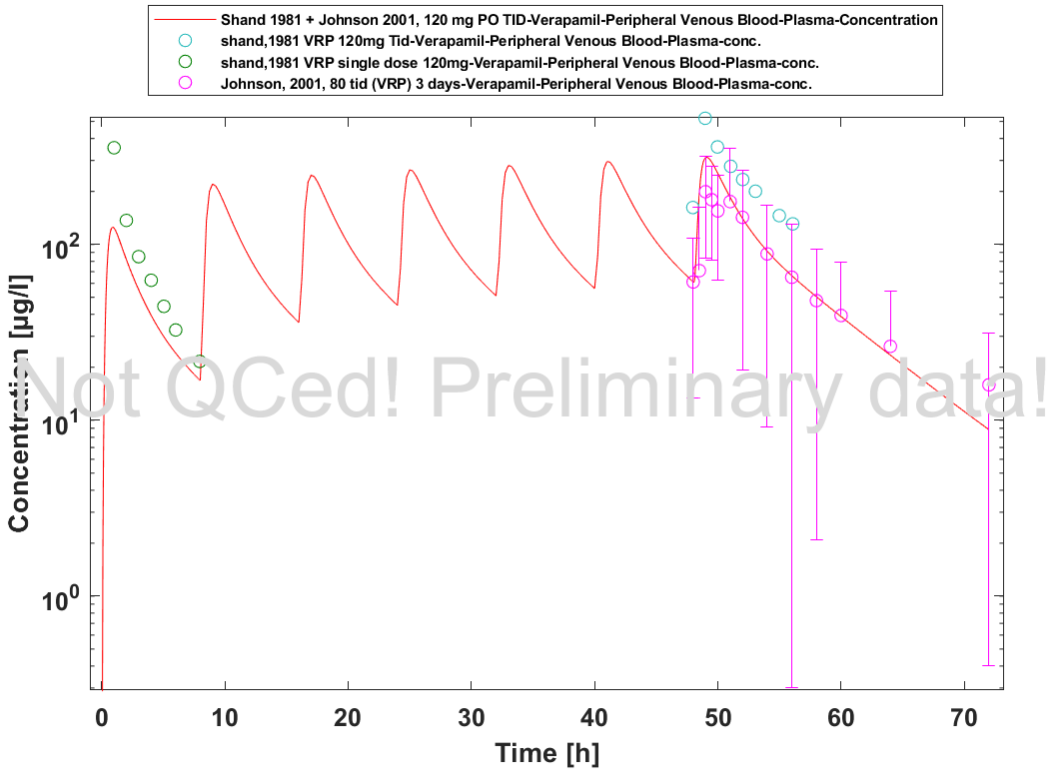

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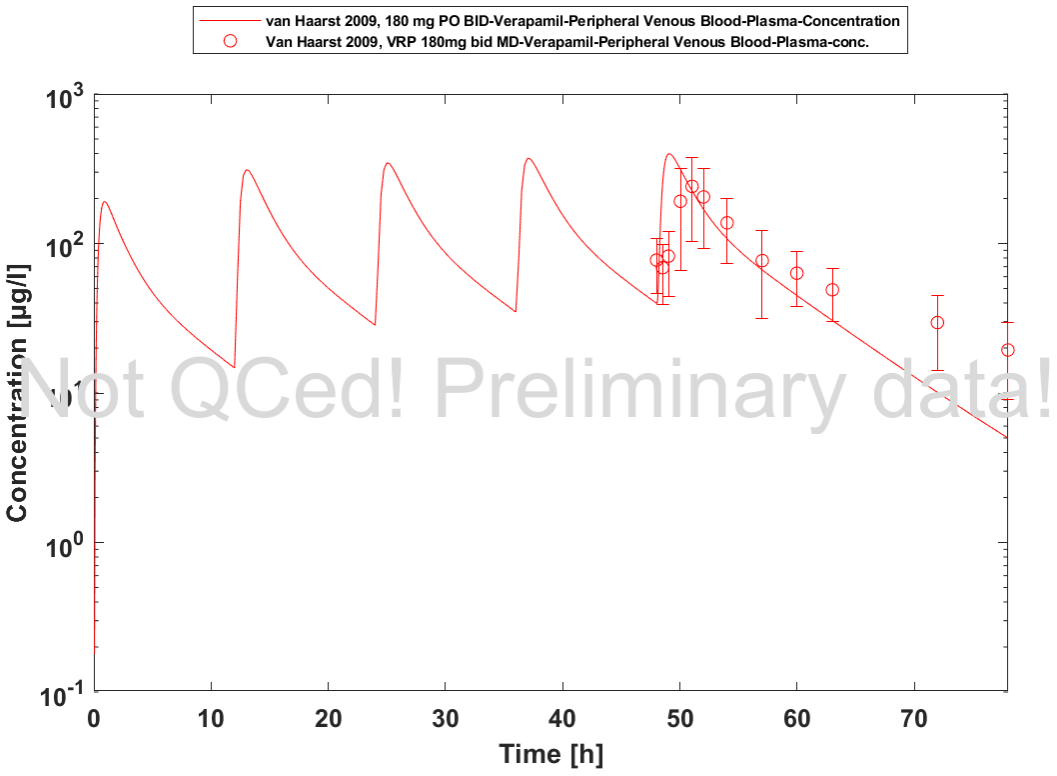

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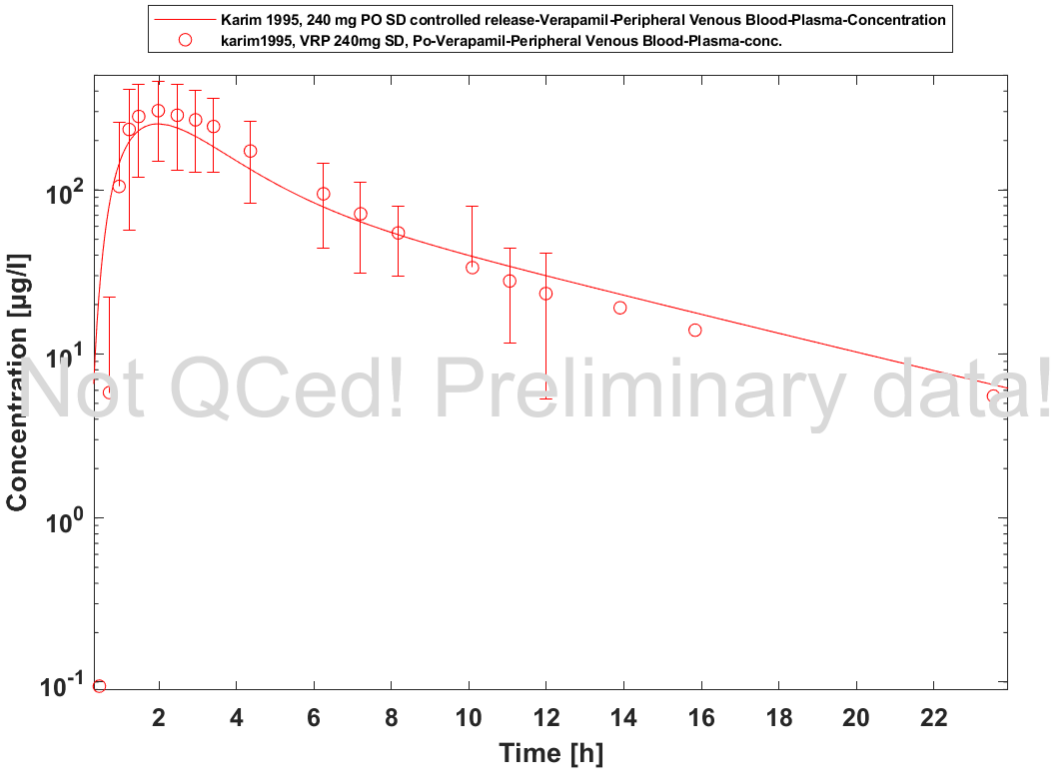

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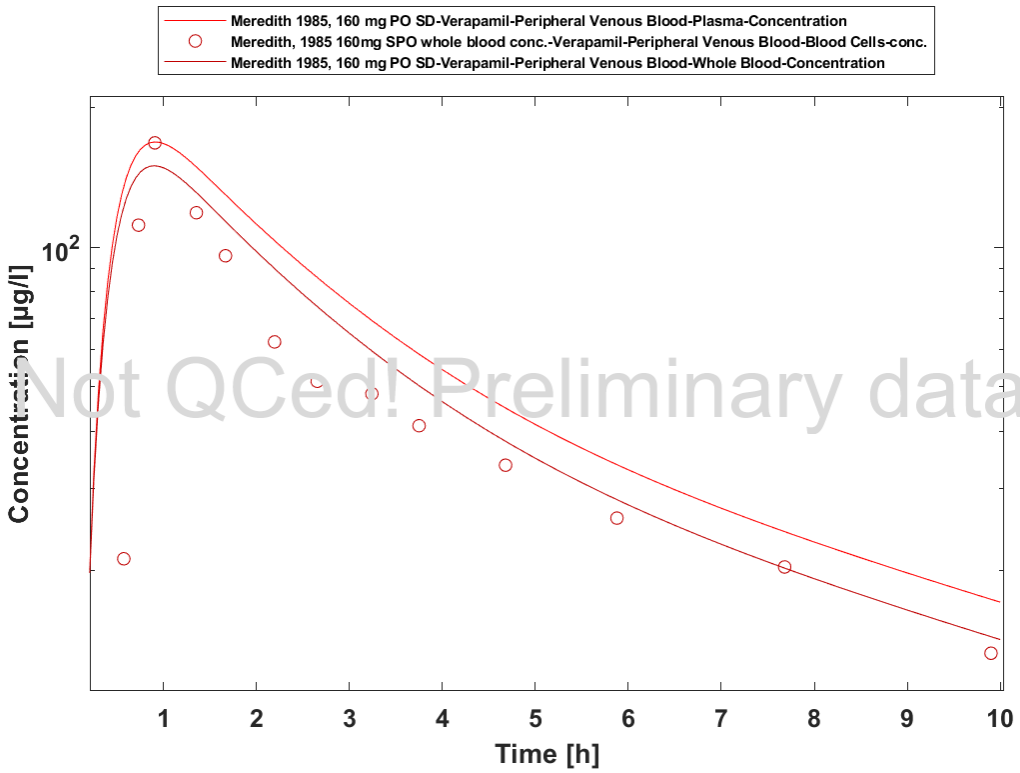

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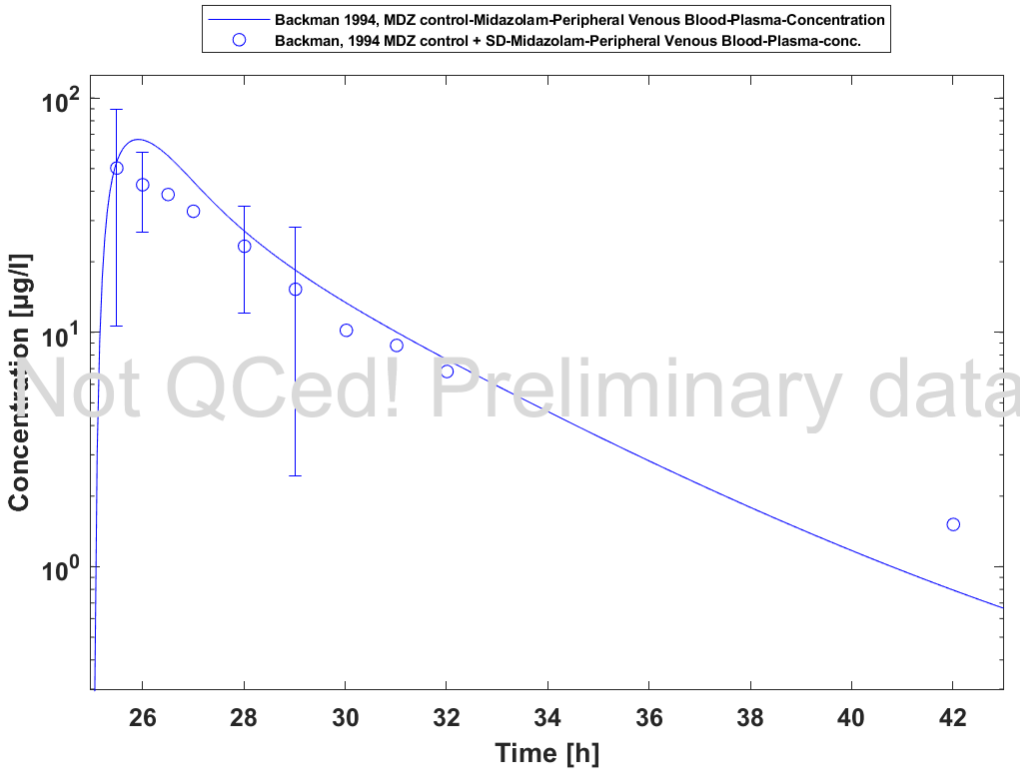

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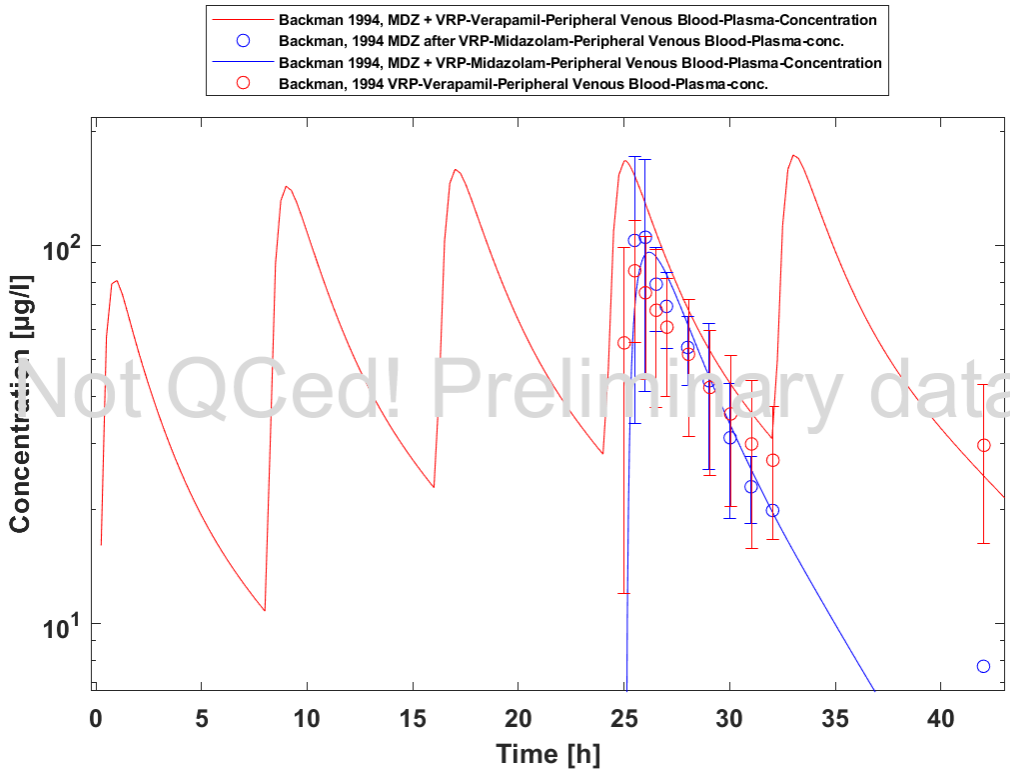

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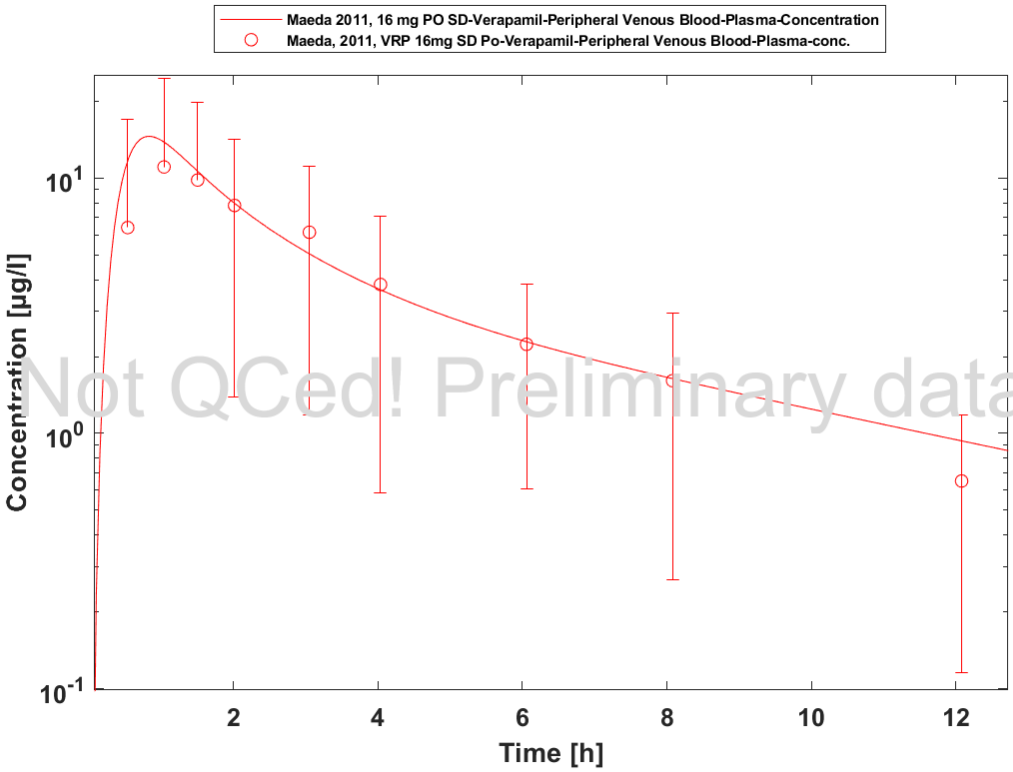

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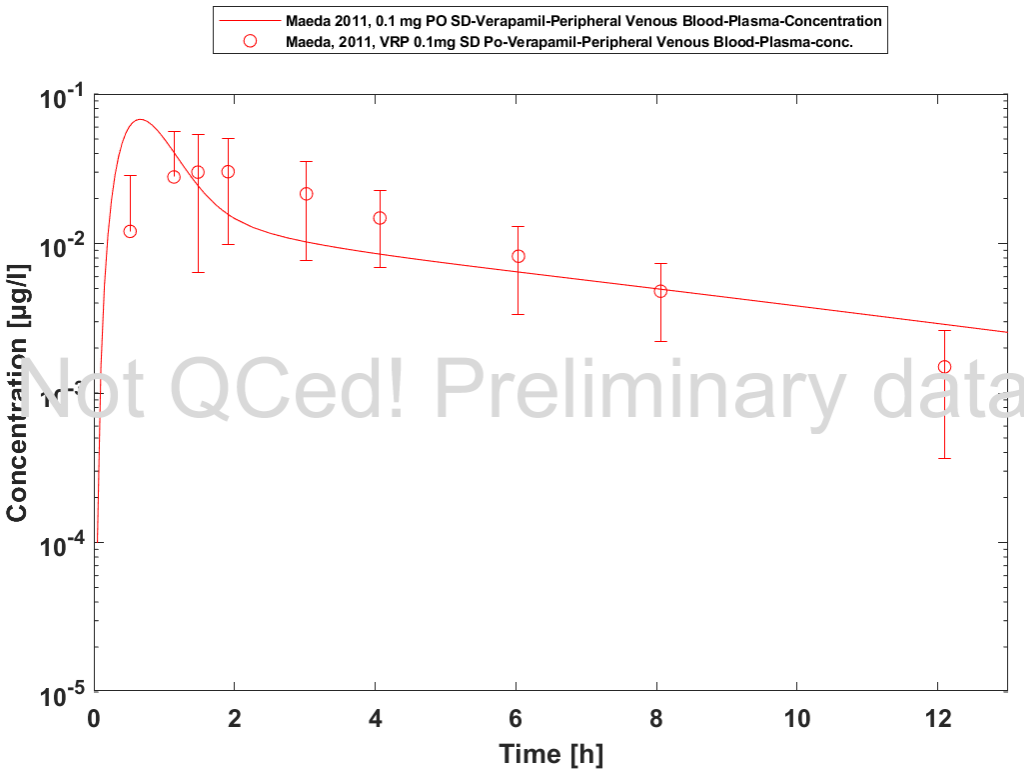

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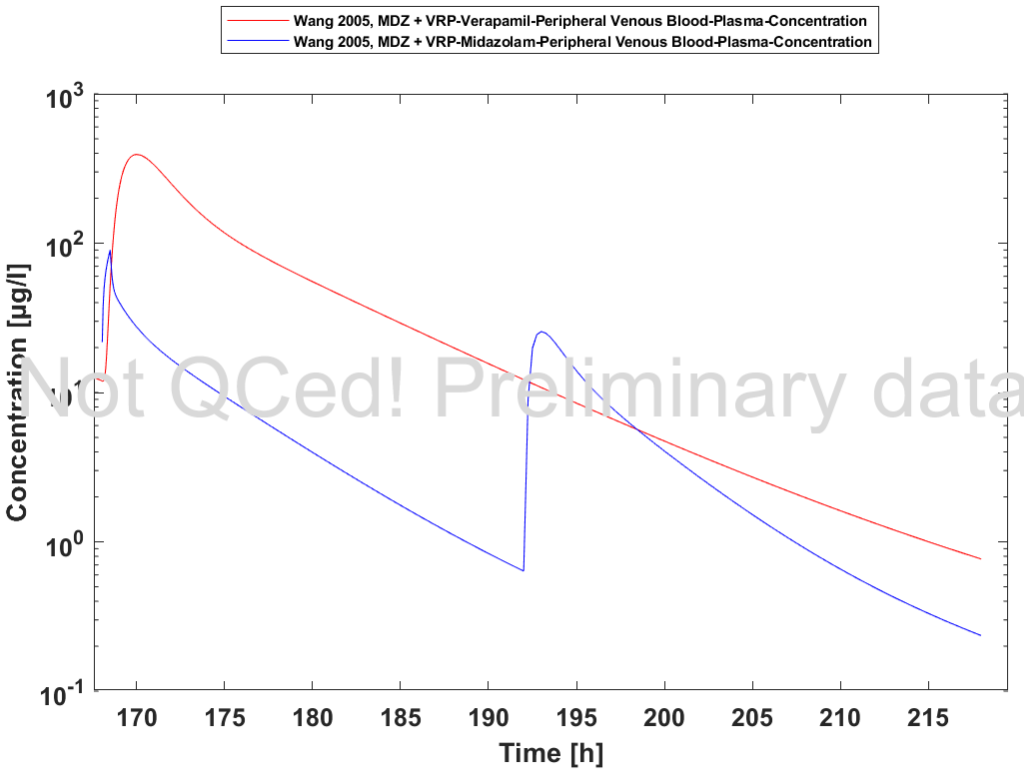

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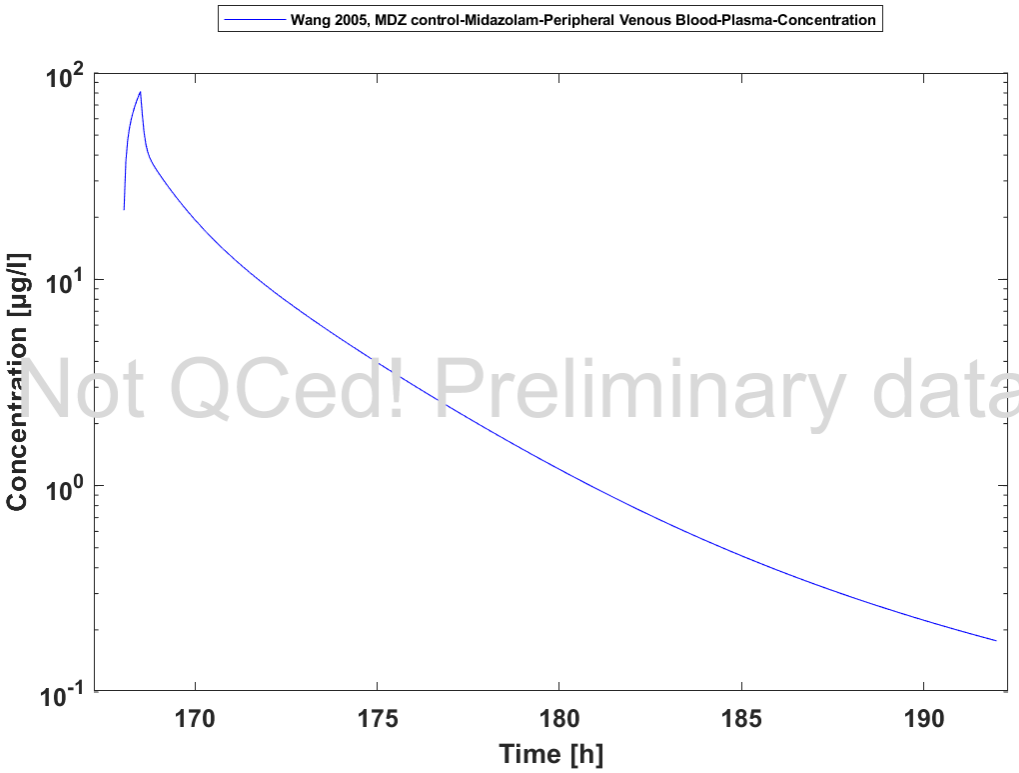

Time Profile Analysis

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of verapamil after single and multiple administration of a variety of doses to healthy adults. Furthermore, CYP3A4 induction on verapamil itself can be described well with the optimized parameterization.

In conclusion, the presented verapamil PBPK model is well-suited to be applied in drug-drug-interaction scenarios.

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