Building and Evaluation of a PBPK Model for Dapagliflozin in Adults

Version	**0.1**
OSP Version	8.0
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1 Introduction

Dapagliflozin is an active, highly selective SGLT2 inhibitor that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary glucose excretion (glucuresis). It is administered orally.

Dapagliflozin is predominantly metabolized by uridine diphosphate-glucuronosyltransferase-1A9 (UGT1A9) in the liver and kidneys to the major metabolite dapagliflozin 3-O-glucuronide and can be considered a sensitive substrate for characterization of UGT1A9 activity. In a clinical drug interaction study, co-administration of mefenamic acid with dapagliflozin resulted in a dapagliflozin AUC ratio of 1.51 and Cmax ratio of 1.13 (Kasichayanula 2013a).

Using published clinical data, the objective is to establish a whole-body PBPK model for dapagliflozin with a quantitative representation of its UGT1A9 metabolism.

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

The presented dapagliflozin PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (https://github.com/Open-Systems-Pharmacology/Dapagliflozin-model).

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. (Kuepfer 2016) 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.

First, a base mean model was built using clinical Phase I data including selected single dose studies with intravenous and oral applications (capsule) of dapagliflozin to find an appropriate structure to describe the pharmacokinetics in plasma. The mean PBPK model was developed using a typical European individual. The relative tissue specific expressions of enzymes predominantly being involved in the metabolism of dapagliflozin (UGT1A9 and UGT2B7,) were considered based on high-sensitive real-time RT-PCR (Nishimura 2013). Absolute tissue specific expressions were obtained by considering the respective absolute concentration in the liver as reported by Ohtsuki *et al.* (Ohtsuki 2012).

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.

Once the appropriate structural model was identified, additional parameters for tablet formulations were identified.

The model was then verified by simulating:

- multiple dose studies
- a food effect study

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	408.873	DrugBank DB06292	Molecular weight
pK_a		12.57	DrugBank DB06292	Acid dissociation constant
Solubility (pH)	mg/mL	0.173 (7)	DrugBank DB06292	Aqueous Solubility
logP		2.7	DrugBank DB06292 (experimental)	Partition coefficient between octanol and water
fu	%	9	Obermeier 2009	Fraction unbound in plasma
B/P ratio		0.88	Obermeier 2009	Blood to plasma ratio

2.2.2 Clinical Data

A literature search was performed to collect available clinical data on dapagliflozin 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
Boulton 2013	14C-dapagliflozin intravenous and Dapagliflozin oral administration
DeFronzo 2013	Healthy subjects with a single oral dose of 10 mg
Imamura 2013	Control phase with a single oral dose of 10 mg
Kasichayanula 2008	Mass balance information
Kasichayanula 2011a	Fasted, single oral dose of 10 mg
Kasichayanula 2011b	Control phases of study 1, 2 and 3 (single oral doses of 20 mg or 50 mg)
Kasichayanula 2011c	Healthy subjects with a single oral dose of 10 mg
Kasichayanula 2012	Control phase with a single oral dose of 20 mg
Kasichayanula 2013a	Control phases of study 1 and 2 (single oral doses of 10 mg)
Kasichayanula 2013b	Healthy subjects with normal kidney function with a single oral dose of 50 mg
Komoroski 2009 and FDA Clinical Pharmacology Review for NDA 202293	SAD 2.5 to 500 mg (fasted)
Vakkalagadda 2016	Dapagliflozin only (single oral dose 10 mg)

Kasichayanula *et al.* (Kasichayanula 2008) investigated the mass balance of dapagliflozin in healthy subjects after a single oral dose of 50 mg. The following table gives an overview of the results:

Output	reported	normalized**
Total recovery after 312 h	96.15%	
Urine	75.16%	
- unchanged	1.20%	1.23%
- as metabolites	72.00%	73.93%
Feces	20.99%	
- unchanged	15.40%	18.90%
- as metabolites	1.70%	2.09%

** to sum up to total excretion of urine and feces, respectively

The metabolic pattern was determined as shown in the following table.

Output	reported	normalized**	add fraction excretion to feces of unchanged dapagliflozin to glucuronides***
Dapagliflozin-3-O-glucuronide	60.70%	61.44%	78.80%
Dapagliflozin-2-O-glucuronide	5.40%	5.47%	7.01%
Dapagliflozin oxidative metabolites	9.00%	9.11%	9.11%
SUM		**76.01%**	**94.92%**

** to sum to the values of metabolic quantifications from the table above (73.93% + 2.09%)

*** The fraction excretion to feces of unchanged dapagliflozin of 18.90% (see above) was added and distributed proportionally to Dapagliflozin-3-O-glucuronide and Dapagliflozin-2-O-glucuronide under the assumption that the measured fraction of unchanged dapagliflozin resulted from originally glucuronidated metabolites that underwent biliary excretion and subsequent degradation to dapagliflozin by bacterial glucurinodases in feces.

The following table shows the final mass balance data used for model building under the assumption of that unchanged dapagliflozin molecules in feces were originally glucuronides. Please refer to Section 2.3 for rationale.

Observer	Value
Fraction excreted to urine of unchanged dapagliflozin	1.23%
Fraction metabolized UGT1A9 (to dapagliflozin-3-O-glucuronide)	78.80%
Fraction metabolized UGT2B7 (to dapagliflozin-3-O-glucuronide)	7.01%
Fraction metabolized to oxidative metabolites	9.11%
SUM	**96.15%**

2.2.2.2 Model Verification

The following studies were used for model verification:

Publication	Arm / Treatment / Information used for model verification
Chang 2015	Study 1 Treatment A (single oral dose of 5 mg as IC tablet) and Study 2 Treatment A (single oral dose of 10 mg as IC tablet)
Komoroski 2009 and FDA Clinical Pharmacology Review for NDA 202293	MAD 2.5 to 100 mg (day 1, 7 and 14)
Komoroski 2009	Single oral dose 250 mg (fed)

2.3 Model Parameters and Assumptions

2.3.1 Absorption

Studies including oral applications of dapagliflozin used for model building applied either a capsule or immediate release tablets. They all demonstrated rapid and extensive absorption. The availability of dense data during absorption, data covering a broad range of doses (from 2.5 up to 500 mg, and intravenous pharmacokinetic data (Boulton 2013) allowed to the identification of the *in vivo* intestinal permeability and an effective *in vivo* solubility in this PBPK model (see also Section 2.3.4).

During model building, two different "data scenarios" regarding mass balance information were tested:

Scenario 1: The measured fraction excreted to feces as unchanged drug of approx. 19% resulted from incomplete absorption (assuming f_a ~ 0.81).

Scenario 2: The measured fraction excretion to feces of unchanged dapagliflozin resulted from originally glucuronidated metabolites that underwent biliary excretion and subsequent degradation to dapagliflozin by bacterial glucurinodases in feces (assuming f_a ~ 1). This phenomenon of cleavage of glucuronides by beta-glucuronidases in the colon of hepatobiliary secreted glucuronides to the aglycone (e.g. parent drug) was reported previously (Blaut 2013, Molly 1993, Possemiers 2004, Sakamoto 2002).

Scenario 1 did not allow to find a good description of the pharmacokinetic data. Thus, scenario 2 was used during further model building. Note that this increased the fraction metabolized via UGT1A9 and UGT2B7.

The dissolution of the tablets from Chang *et al.* (Chang 2015) - referenced as individual component (IC) tablets - were implemented via an empirical Weibull dissolution tablet. The respective parameters were identified via manual sensitivity analysis.

2.3.2 Distribution

Dapagliflozin is moderately protein bound (91 %) in plasma (Kasichayanula 2014). This value was used in this PBPK model. It was assumed that the major binding partner is albumin.

An important parameter influencing the resulting volume of distribution is lipophilicty. The reported experimental logP value of 2.7 (DrugBank DB06292) served as a starting value. Finally, the model parameters `Lipophilicity` and `logP (veg.oil/water)` were optimized to match best clinical data (see also Section 2.3.4).

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`. The specific organ permeability was also optimized to match best clinical data (see also Section 2.3.4).

The reported blood to plasma ratio of 0.88 (Obermeier 2009) was fixed in the model.

2.3.3 Metabolism and Elimination

As previously described in Section 2.2.2, mass balance data (Kasichayanula 2008, Obermeier 2009, Kasichayanula 2014) indicated that UGT1A9 is predominatly responsible for the metabolism of dapagliflozin. UGT2B7 and some oxidative cyotochrome-P450 enzymes play additional but minor roles.

In summary, three metabolic first order routes were implement into the model:

- UGT1A9 specific clearance
- UGT2B7 specific clearance
- an unspecific hepatic oxidative clearance ("Hepatic-CYP") (The hypothetical lumped Hepatic-CYP enzyme was assumed to be expressed only in the liver with a reference concentration of 1 µmol/L.)

Additionally, a renal clearance (assumed to be mainly driven by glomerular filtration) was implemented.

This clearance and excretion pathways were quantified during parameter optimization to best match clinical data (see also Section 2.2.2, Section 2.3.1, and Section 2.3.4).

2.3.4 Automated Parameter Identification

This is the result of the final parameter identification.

Model Parameter	Optimized Value	Unit
`Lipophilicity`	2.672	Log Units
`logP (veg.oil/water)`	2.083	Log Units
`Permeability`	3.75E-04	cm/min
`Specific intestinal permeability`	3.97E-05	cm/min
`Solubility at reference pH`	0.221	mg/ml
`CLspec/[Enzyme]` (UGT1A9)	0.399	l/µmol/min
`CLspec/[Enzyme]` (UGT2B7)	6.60E-03	l/µmol/min
`CLspec/[Enzyme]` (Hepatic-CYP)	0.143	l/µmol/min
`GFR fraction`	0.79	
`Blood/Plasma concentration ratio`	0.88 FIXED	

3 Results and Discussion

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

The model was evaluated covering data from studies including in particular

- intravenous and oral administrations.
- single and multiple doses.
- a dose range of 2.5 to 500 mg.
- fasted and fed state administrations.

The model quantifies metabolism via UGT1A9 and UGT2B7.

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: Dapagliflozin

Parameters

Name	Value	Value Origin	Alternative	Default	

Name	Value	Value Origin	Alternative	Default	
Solubility at reference pH	0.2210041453 mg/ml	Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-23 15:34	Water solubility	True	
Reference pH	7	Database-DrugBank DB06292	Water solubility	True	
Lipophilicity	2.6719093089 Log Units	Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-23 15:34	Optimized	True	
Fraction unbound (plasma, reference value)	0.09	Publication-Kasichayanula et al. 2014	Human	True	
Permeability	0.00037527645658 cm/min	Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-23 15:34	Optimized	False	
Specific intestinal permeability (transcellular)	3.9684694792E-05 cm/min	Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-23 15:34	Optimized	False	
Cl	1				
Is small molecule	Yes				

Name	Value	Value Origin	Alternative	Default	
Molecular weight	408.873 g/mol				
Plasma protein binding partner	Albumin				

Calculation methods

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

Processes

Metabolizing Enzyme: UGT1A9-Optimized

Molecule: UGT1A9 Metabolite: Dapagliflozin-3-O-glucuronide

Parameters

Name	Value	Value Origin	
Enzyme concentration	1 µmol/l		
Specific clearance	0 1/min		
CLspec/[Enzyme]	0.399443557 l/µmol/min	Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-23 15:34	

Metabolizing Enzyme: UGT2B7-Optimized

Molecule: UGT2B7 Metabolite: Dapagliflozin-2-O-glucuronide

Parameters

Name	Value	Value Origin	
Enzyme concentration	1 µmol/l		
Specific clearance	0 1/min		

Name	Value	Value Origin	
CLspec/[Enzyme]	0.0066043366201 l/µmol/min	Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-23 15:34	

Systemic Process: Glomerular Filtration-assumed

Species: Human

Parameters

Name	Value	Value Origin	
GFR fraction	0.7899801465	Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-23 15:34	

Metabolizing Enzyme: Hepatic-CYP-Optimized

Molecule: Hepatic-CYP

Parameters

Name	Value	Value Origin	
Enzyme concentration	1 µmol/l		
Specific clearance	0 1/min		
CLspec/[Enzyme]	0.1432967727 l/µmol/min	Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-23 15:34	

Formulation: Dissolved

Type: Dissolved

Formulation: IC tablet (Chang 2015)

Type: Weibull

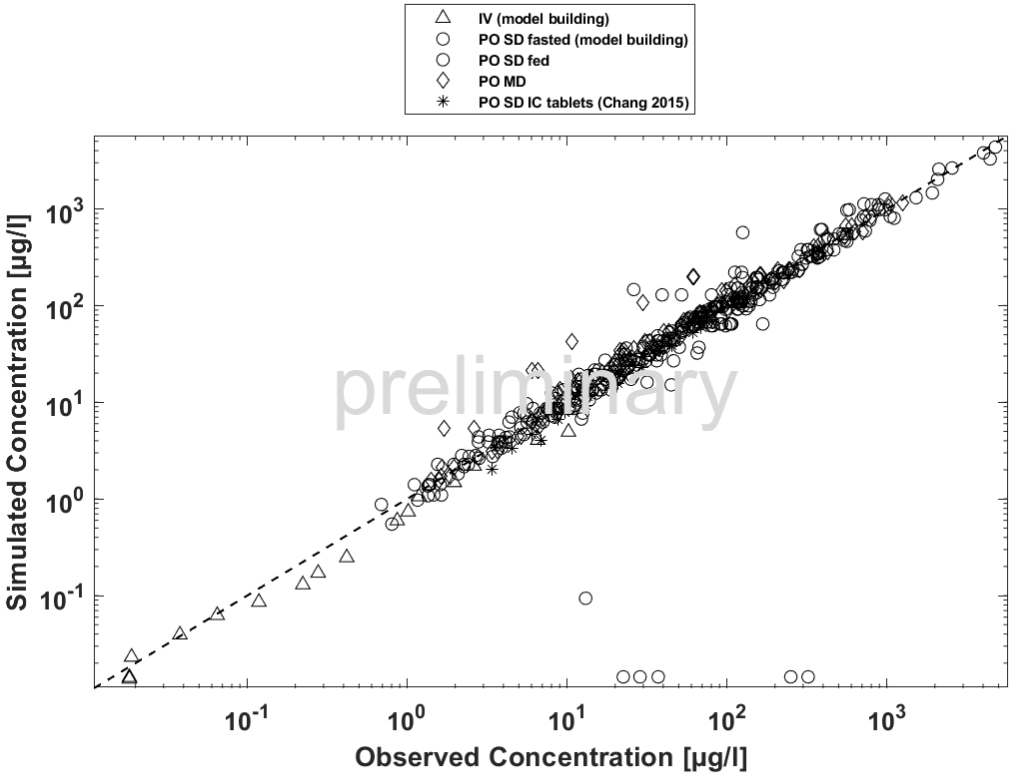
Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	30 min		
Lag time	0 min		
Dissolution shape	0.6		
Use as suspension	Yes		

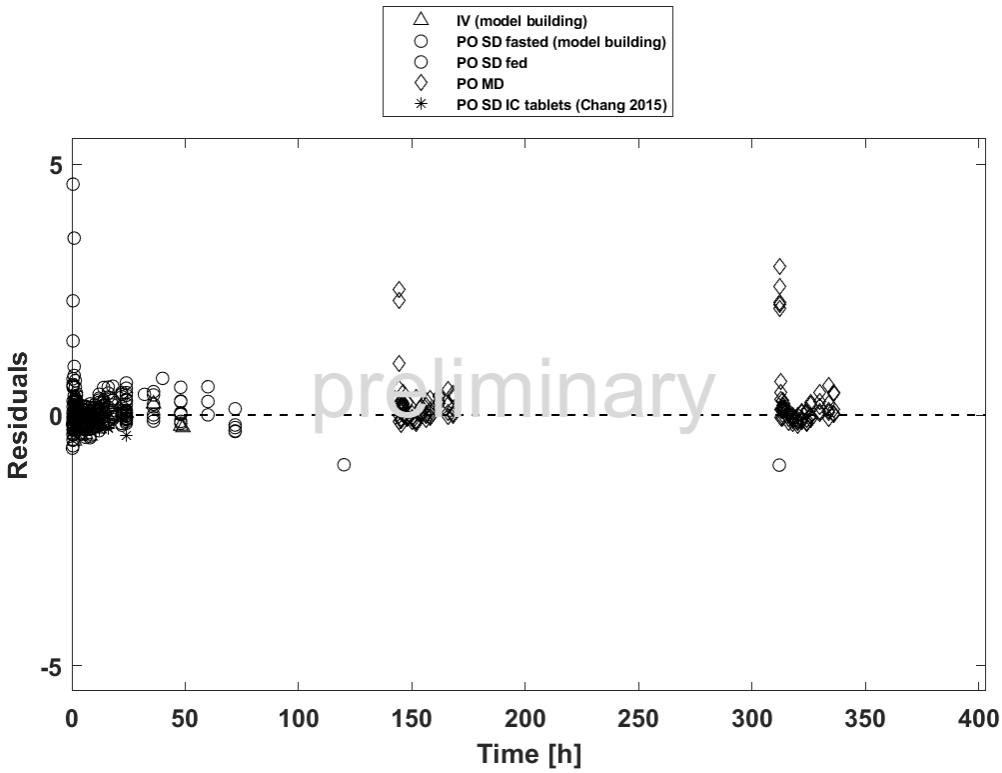
3.2 Diagnostics Plots

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 plot for concentration in plasma



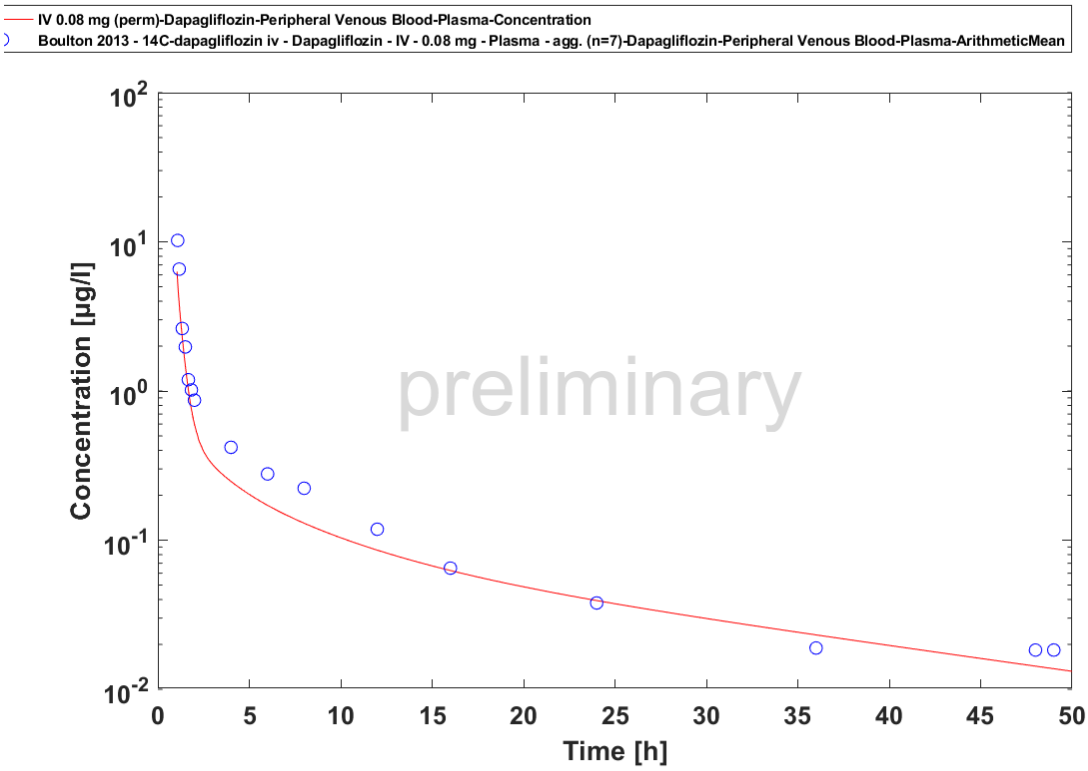
Goodness of fit plot for concentration in plasma

GMFE = 1.343039

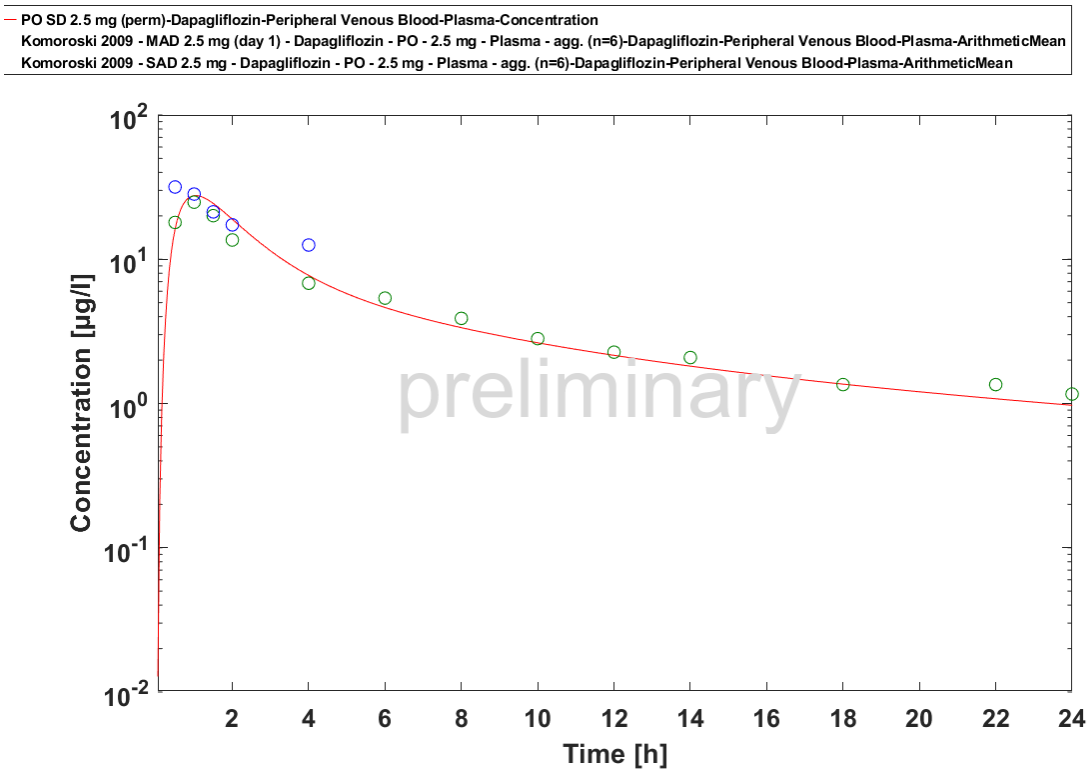
3.3: Concentration-Time Profiles

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

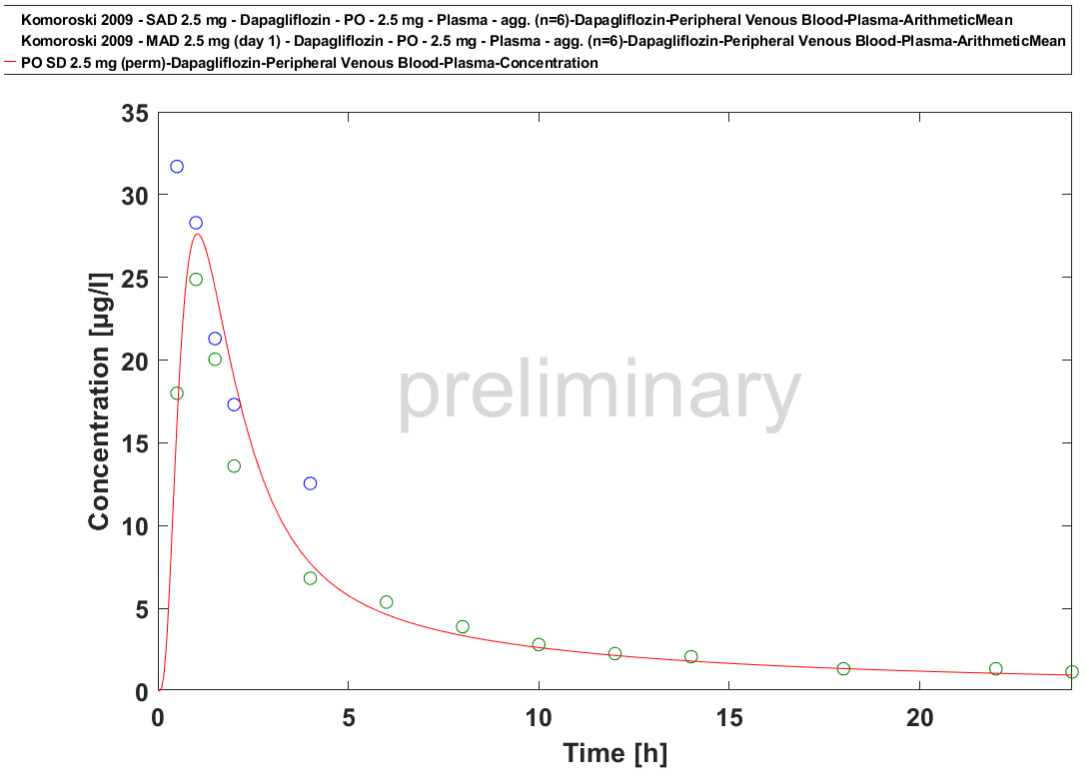
3.3.1 Model Building



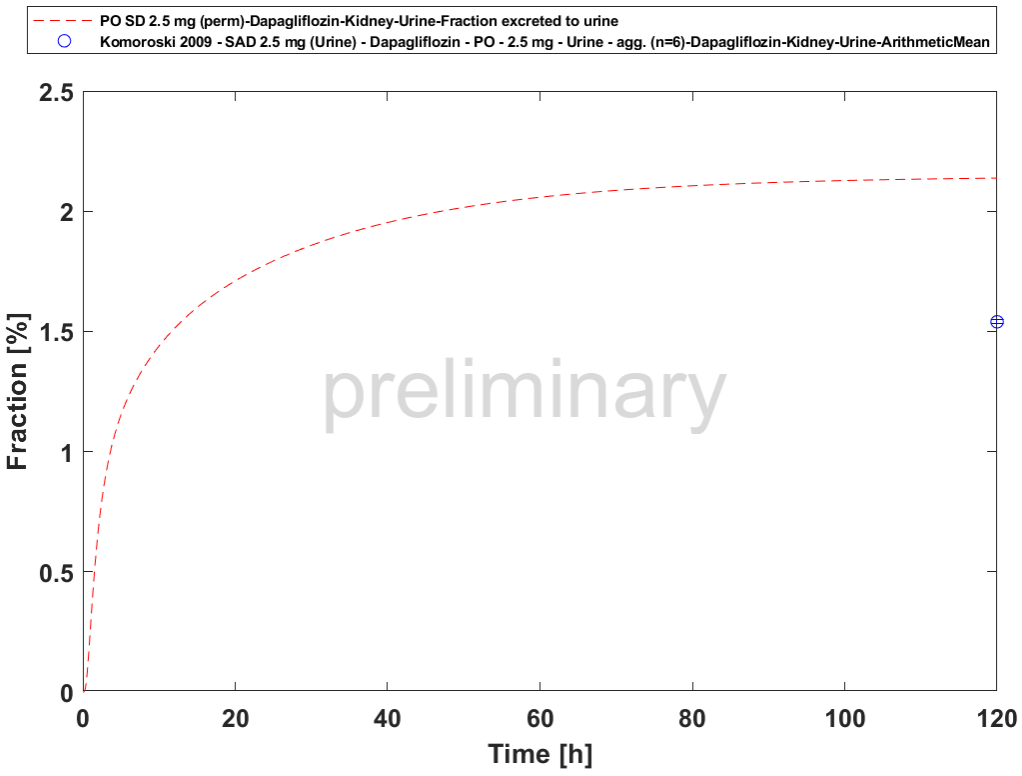
IV 0.08 mg (perm) (log)



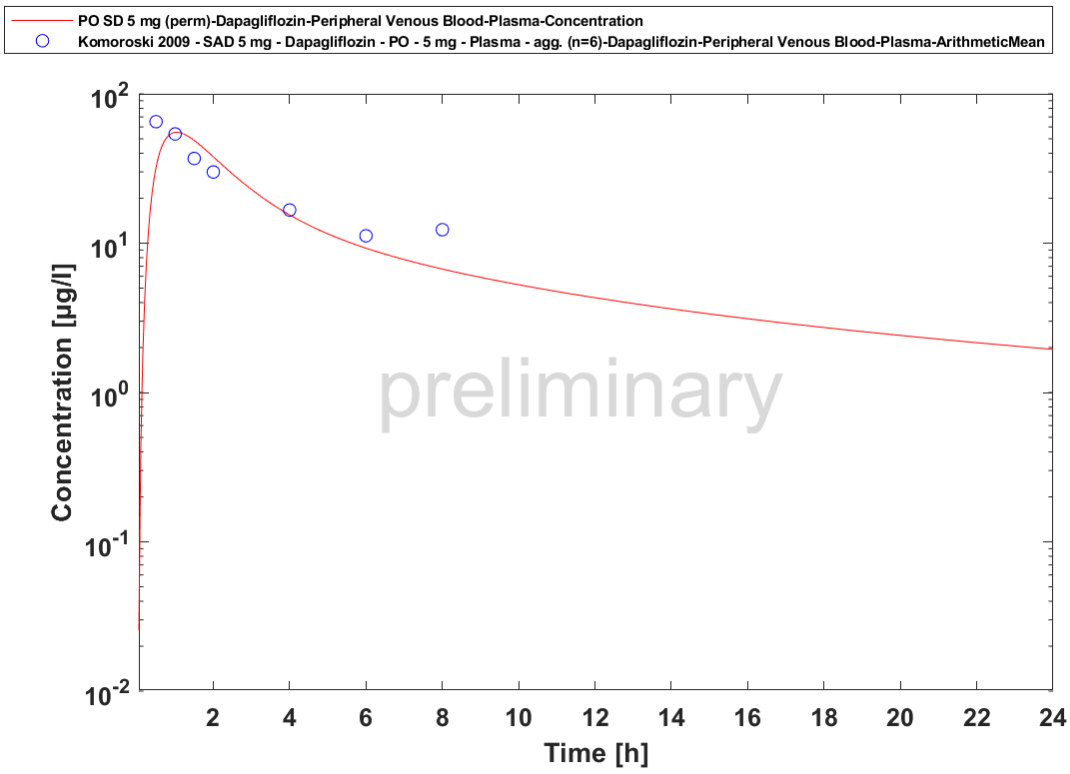
PO SD 2.5 mg (perm) (log)



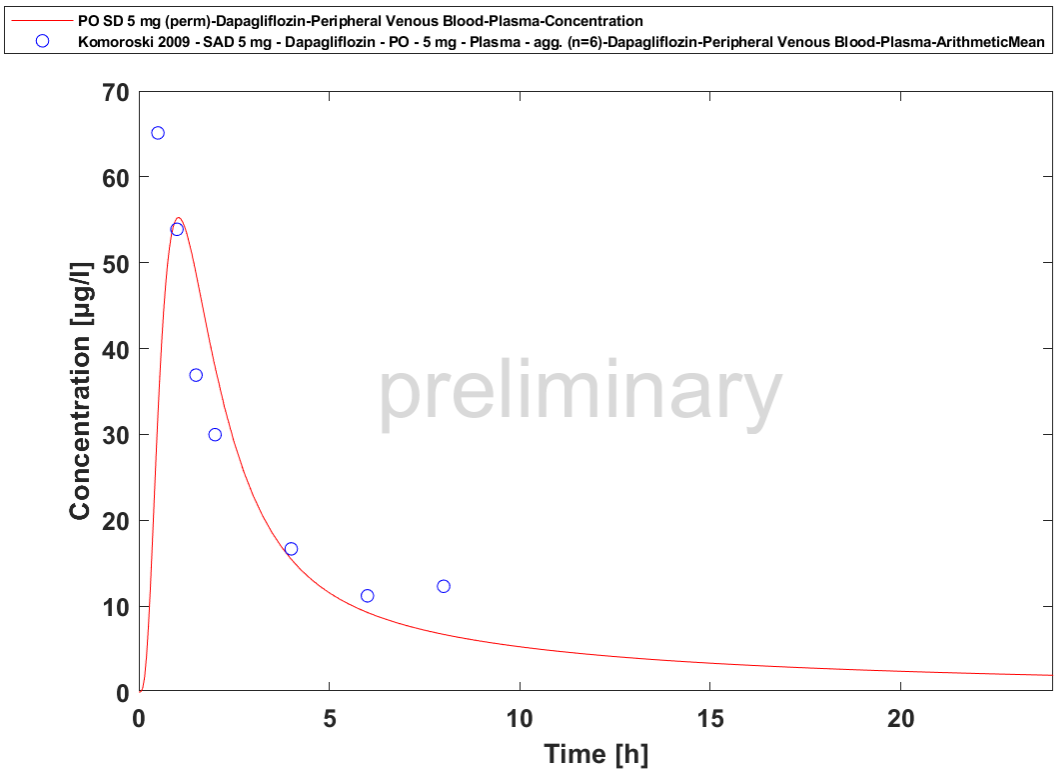
PO SD 2.5 mg (perm) (lin)



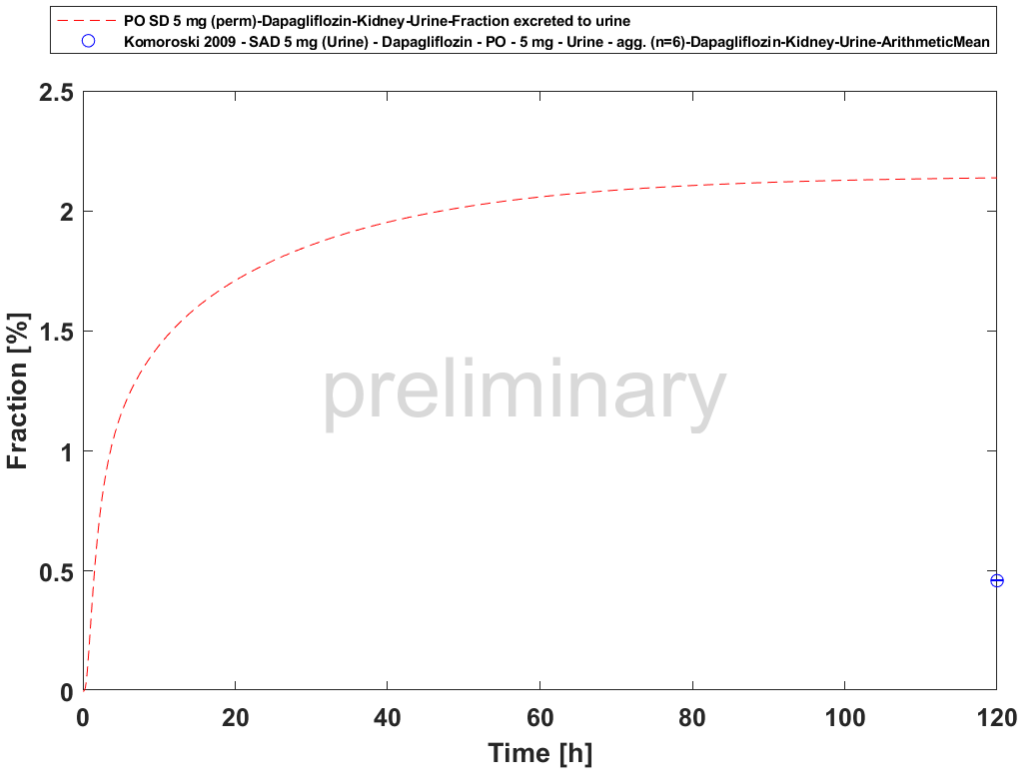
PO SD 2.5 mg (perm) (urinary excretion)



PO SD 5 mg (perm) (log)

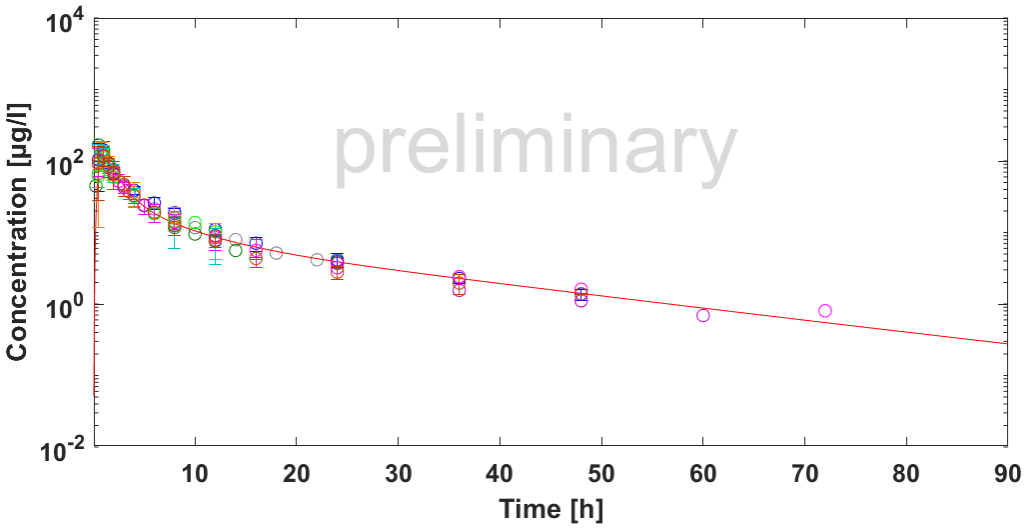


PO SD 5 mg (perm) (lin)



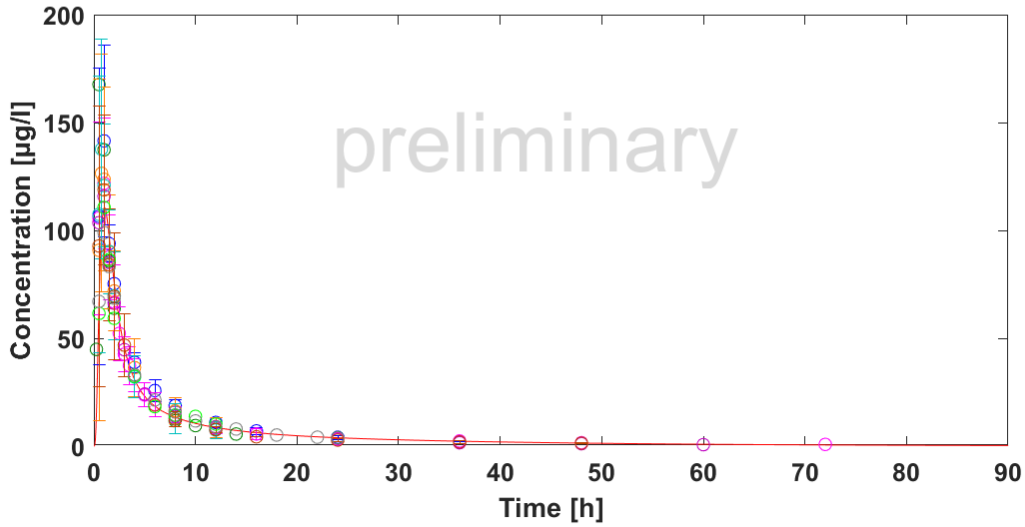
PO SD 5 mg (perm) (urinary excretion)

) 10 mg (day 1) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
iflozin po - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=7)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
ol (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=22)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
)apagliflozin-Peripheral Venous Blood-Plasma-Concentration
- fasted - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=14)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
- Study 1: Control (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=14)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
- Study 2: Control (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=16)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
)apagliflozin - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=42)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
) 10 mg - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
- Healthy Volunteers - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean

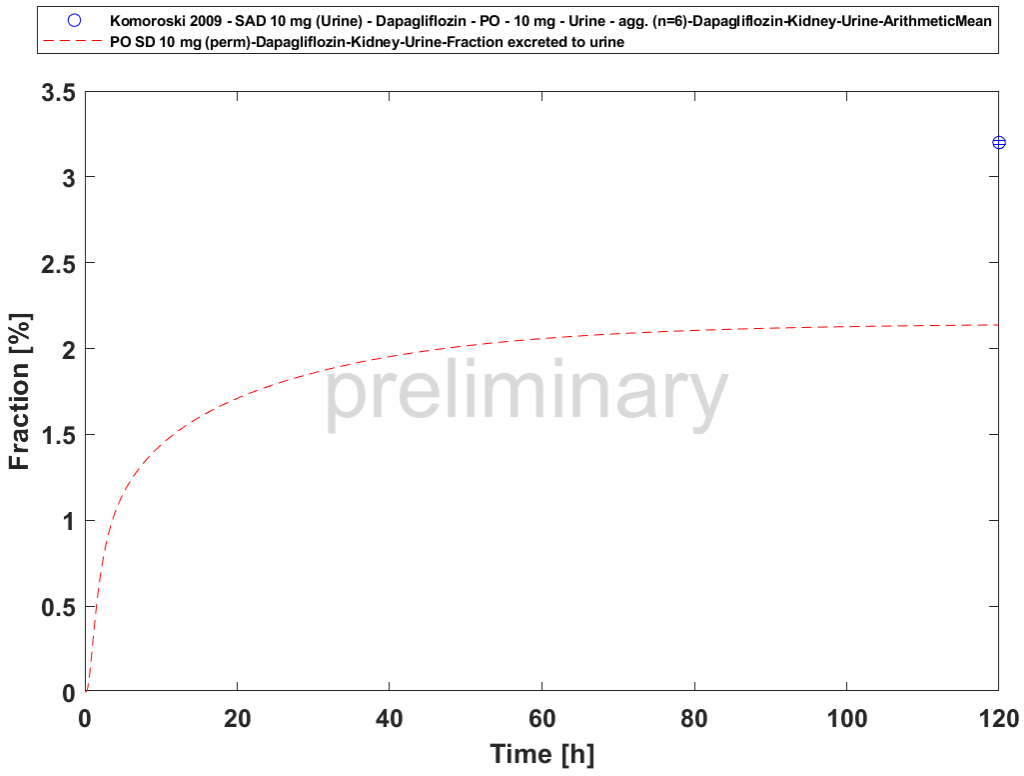


PO SD 10 mg (perm) (log)

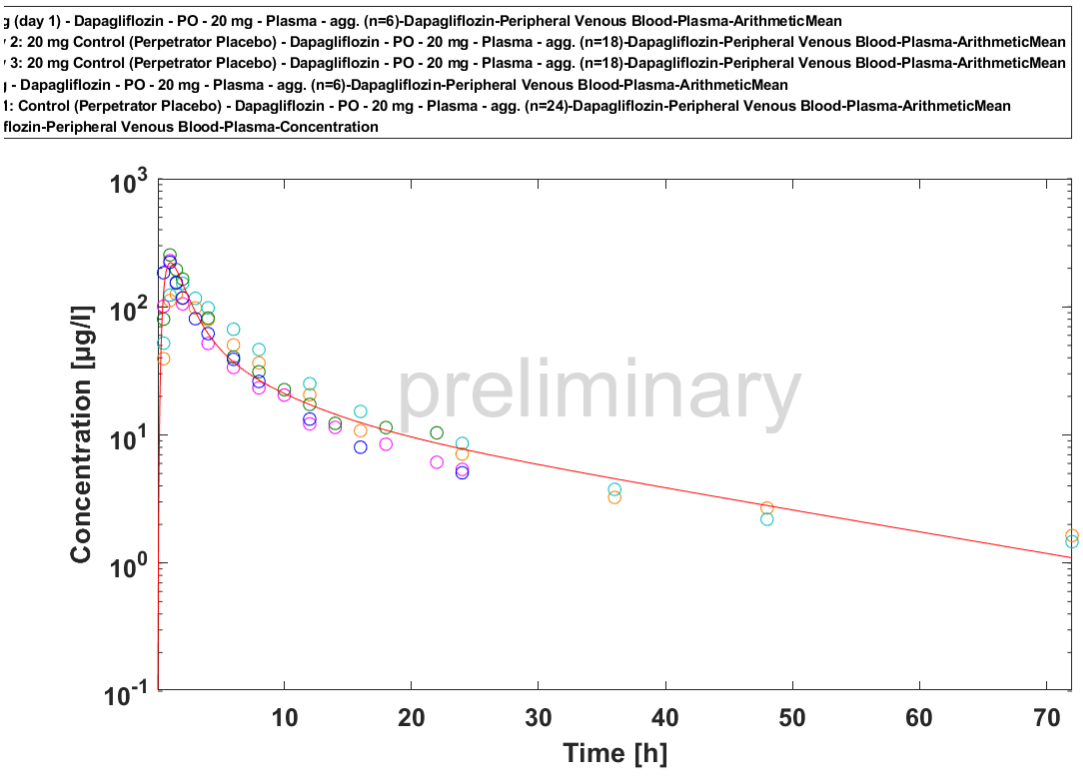
)apagliflozin-Peripheral Venous Blood-Plasma-Concentration
iflozin po - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=7)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
ol (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=22)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
- fasted - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=14)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
- Study 1: Control (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=14)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
- Study 2: Control (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=16)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
)apagliflozin - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=42)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
- Healthy Volunteers - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
) 10 mg - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
) 10 mg (day 1) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



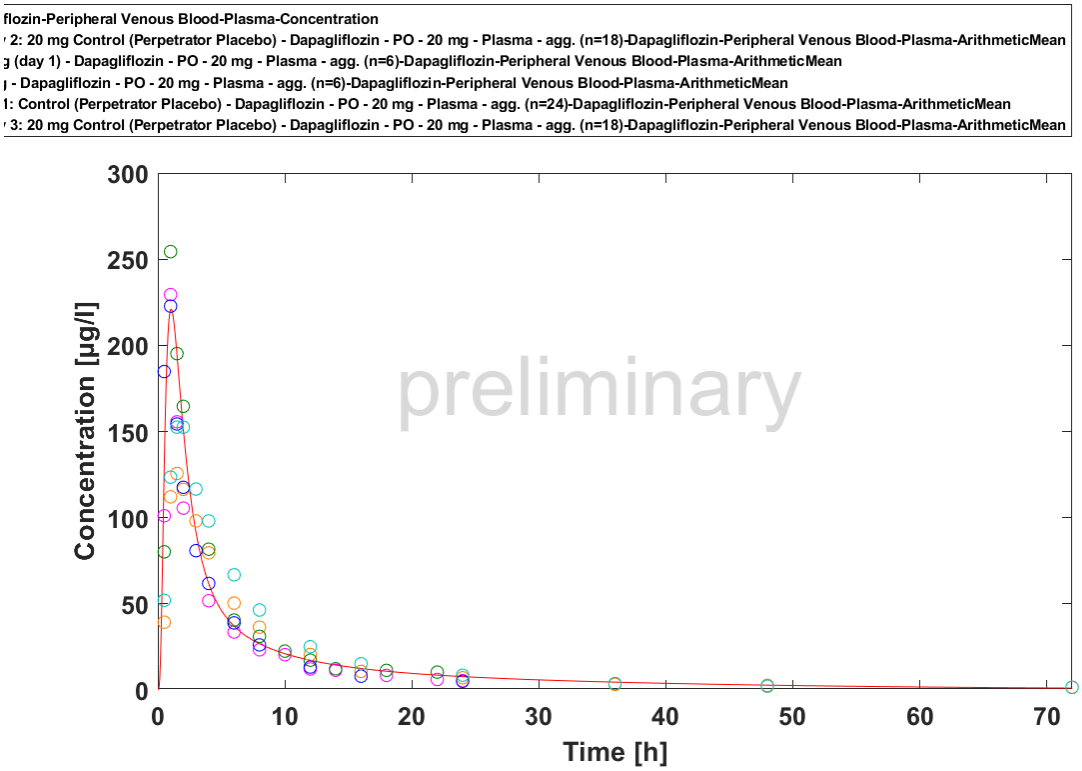
PO SD 10 mg (perm) (lin)



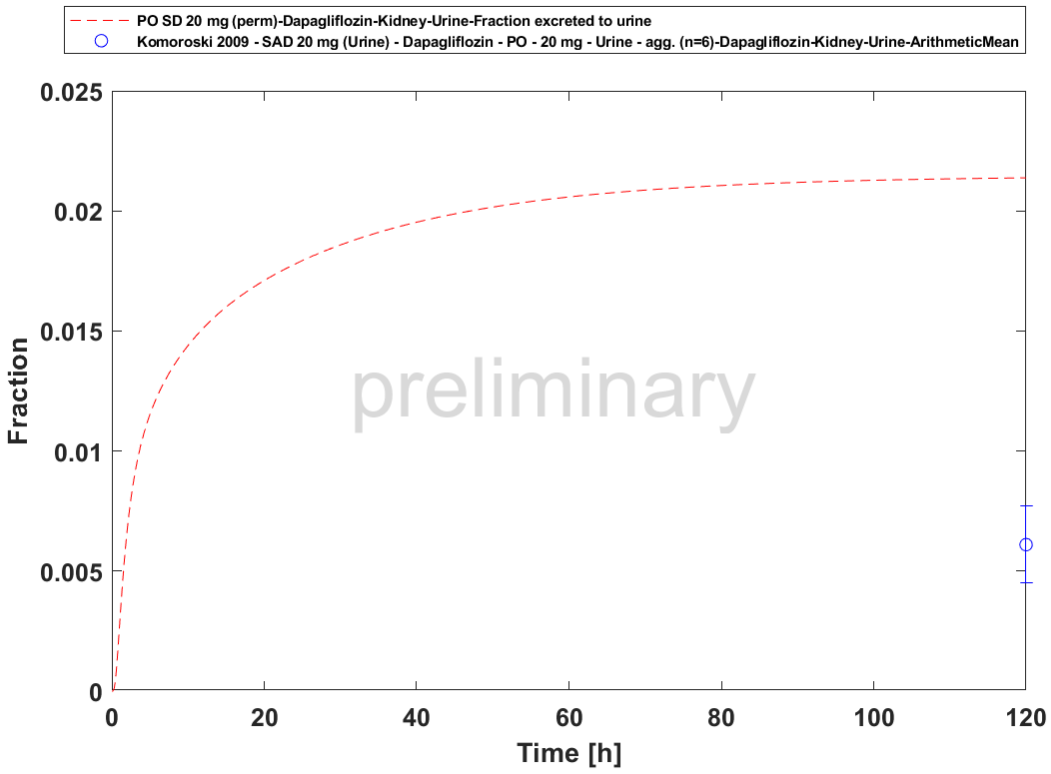
PO SD 10 mg (perm) (urinary excretion)



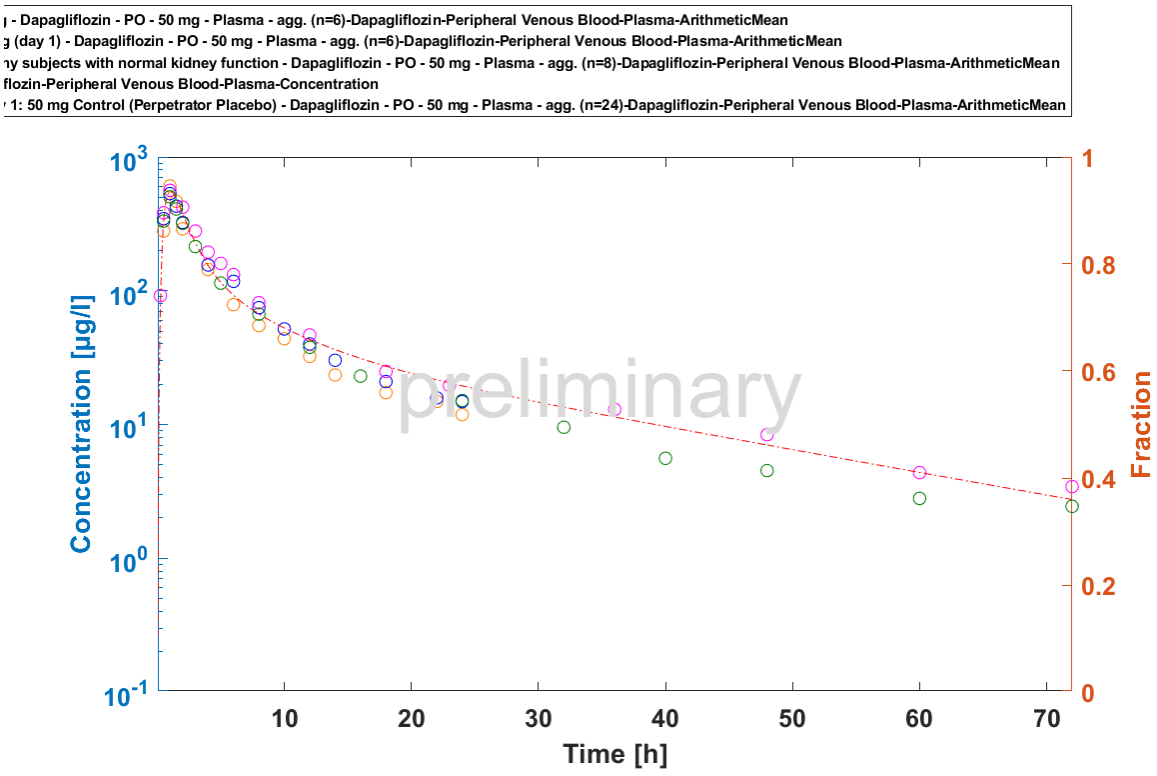
PO SD 20 mg (perm) (log)



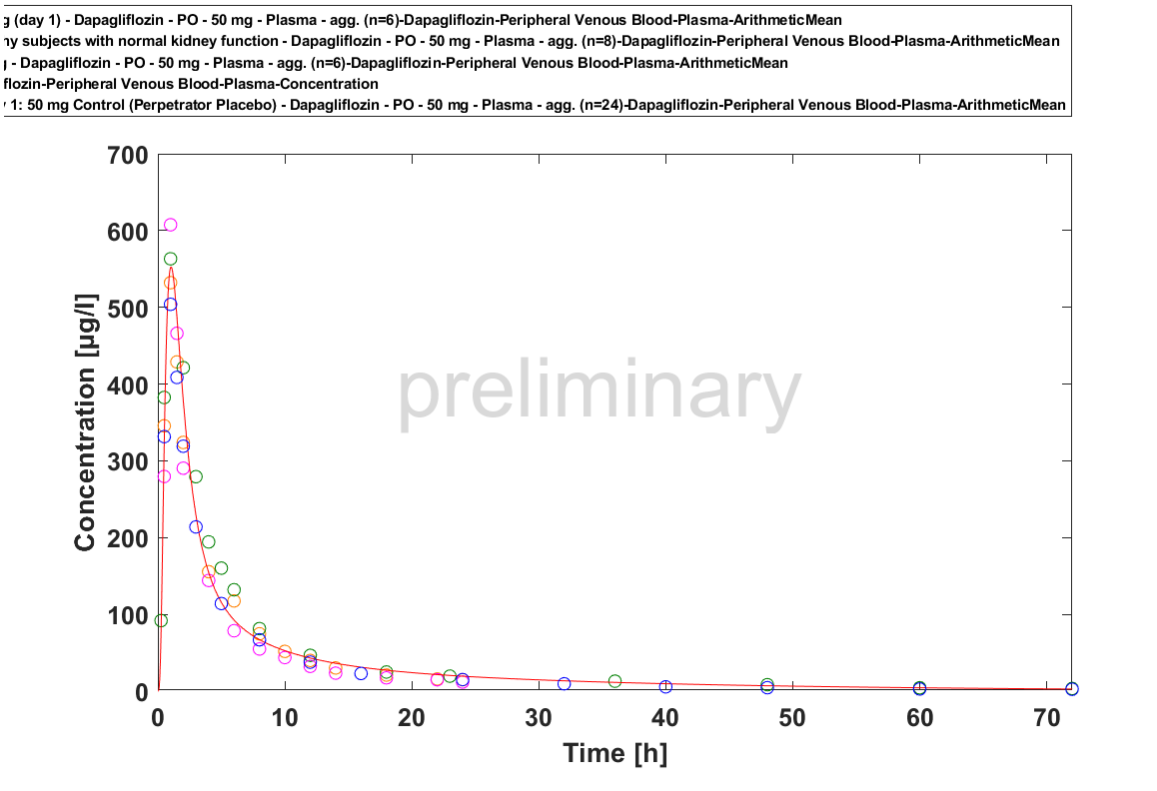
PO SD 20 mg (perm) (lin)



PO SD 2.5 mg (perm) (urinary excretion)



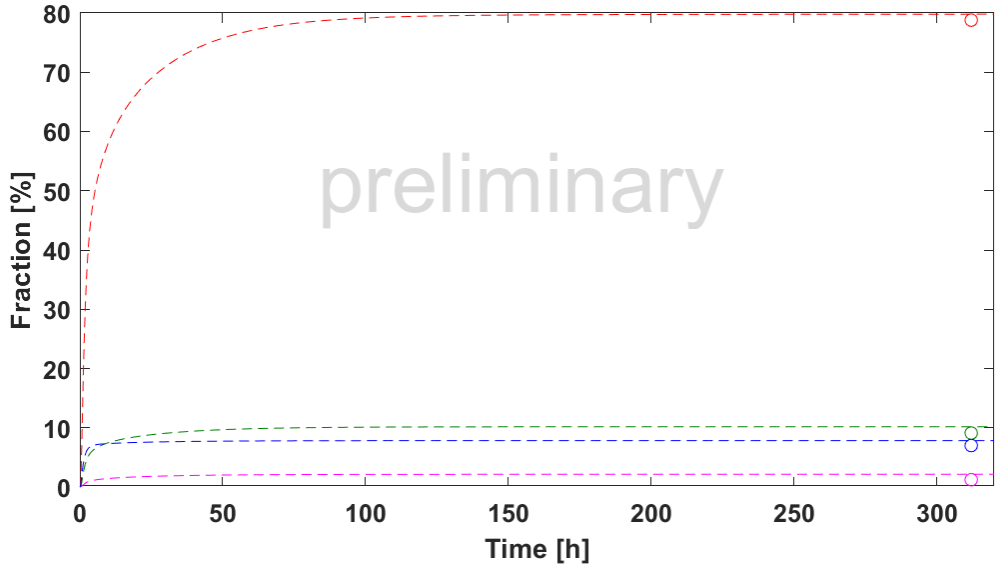
PO SD 50 mg (perm) (log)



PO SD 50 mg (perm) (lin)

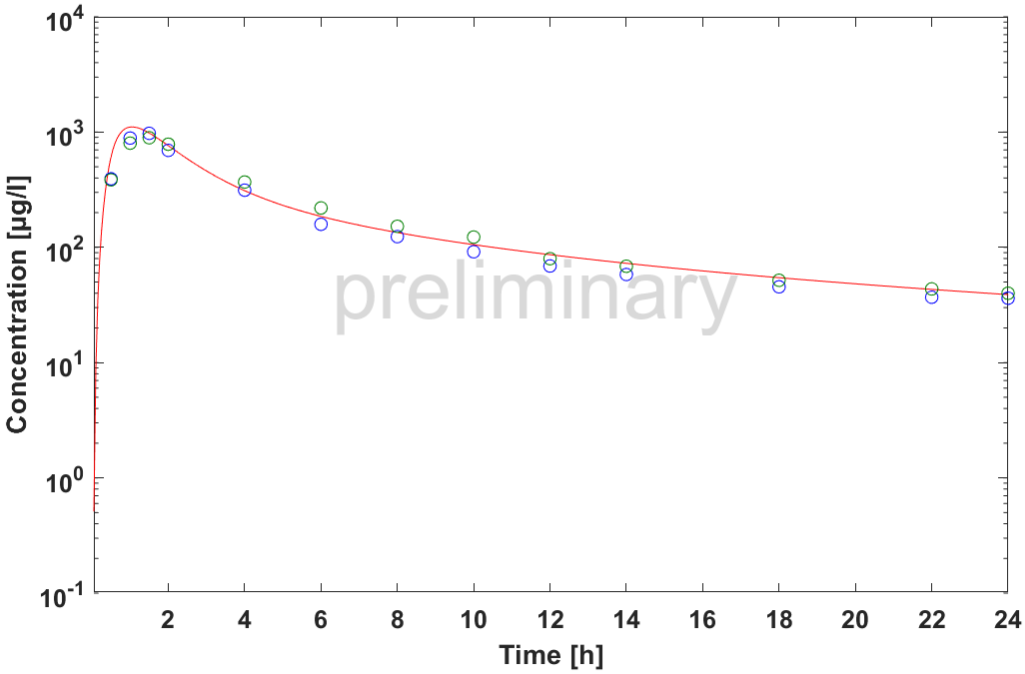
ɔzin oxidative metabolites - PO - 50 mg - Fraction - agg. (n=6)-Dapagliflozin oxidative metabolites-Undefined-Undefined-ArithmeticMean
ŋged feces exret.) - Dapagliflozin-3-O-glucuronide - PO - 50 mg - Fraction - agg. (n=6)-Dapagliflozin-3-O-glucuronide-Undefined-Undefined-ArithmeticMean
ı-Total fraction of dose-Dapagliflozin
:al fraction of dose-Dapagliflozin
ŋged feces exret.) - Dapagliflozin-2-O-glucuronide - PO - 50 mg - Fraction - agg. (n=6)-Dapagliflozin-2-O-glucuronide-Undefined-Undefined-ArithmeticMean

:al fraction of dose-Dapagliflozin
PO - 50 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean

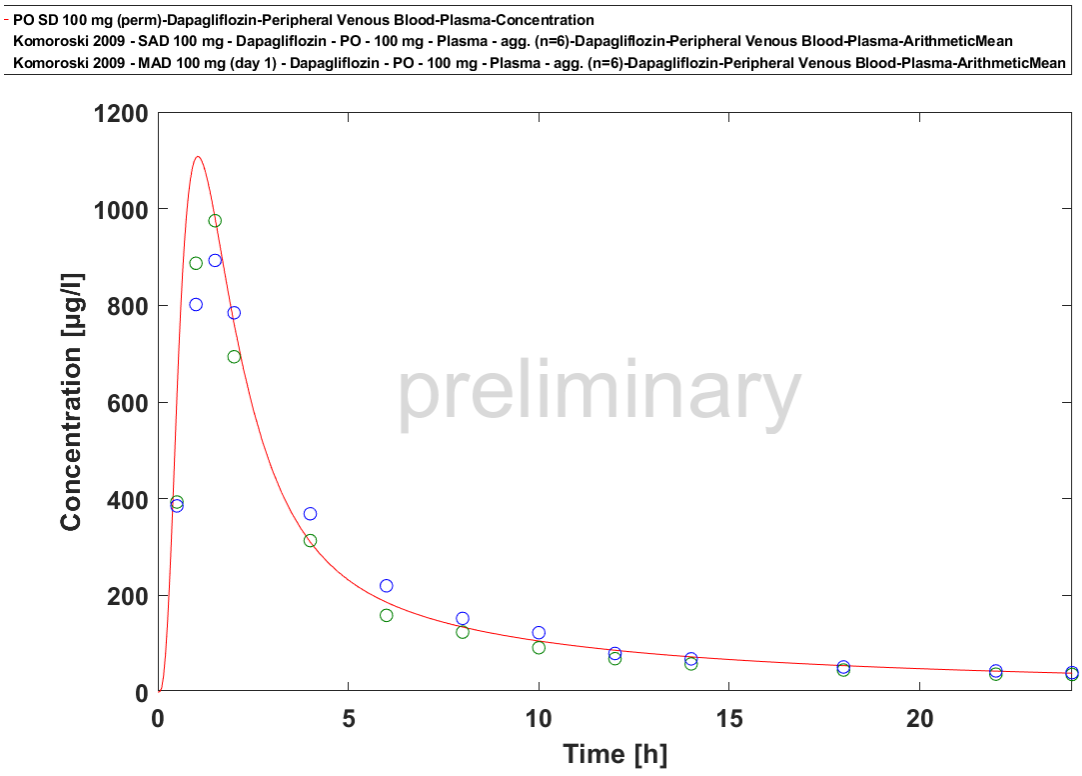


PO SD 50 mg (perm) (fraction excreted/metabolized)

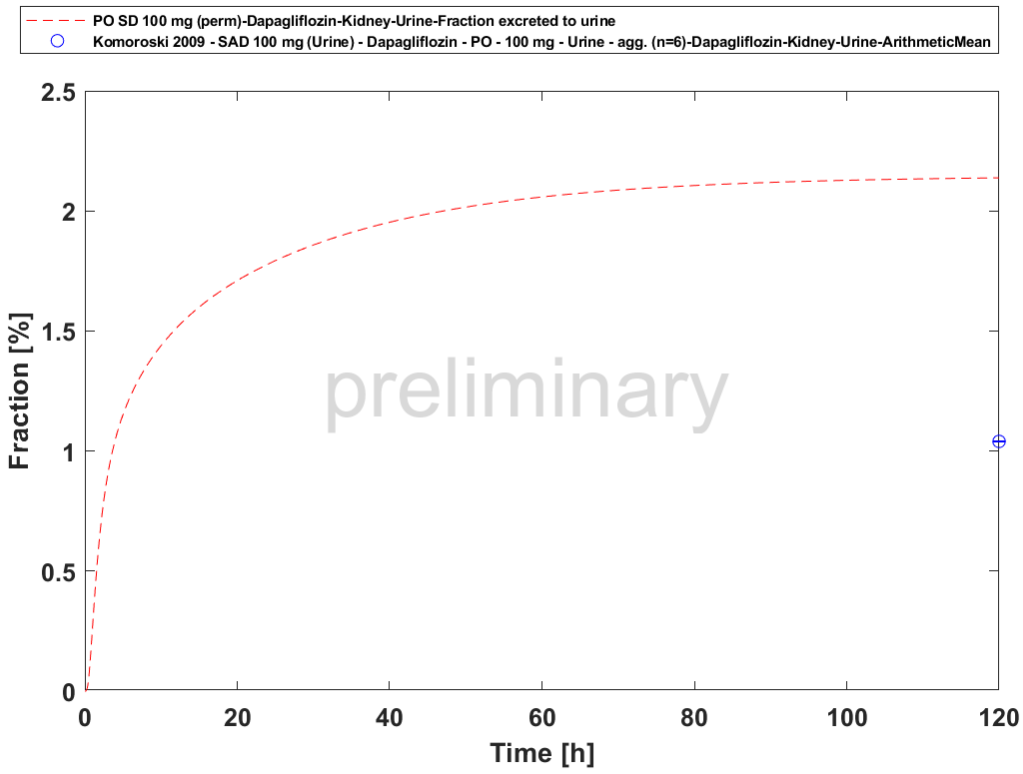
PO SD 100 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Komoroski 2009 - SAD 100 mg - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
Komoroski 2009 - MAD 100 mg (day 1) - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



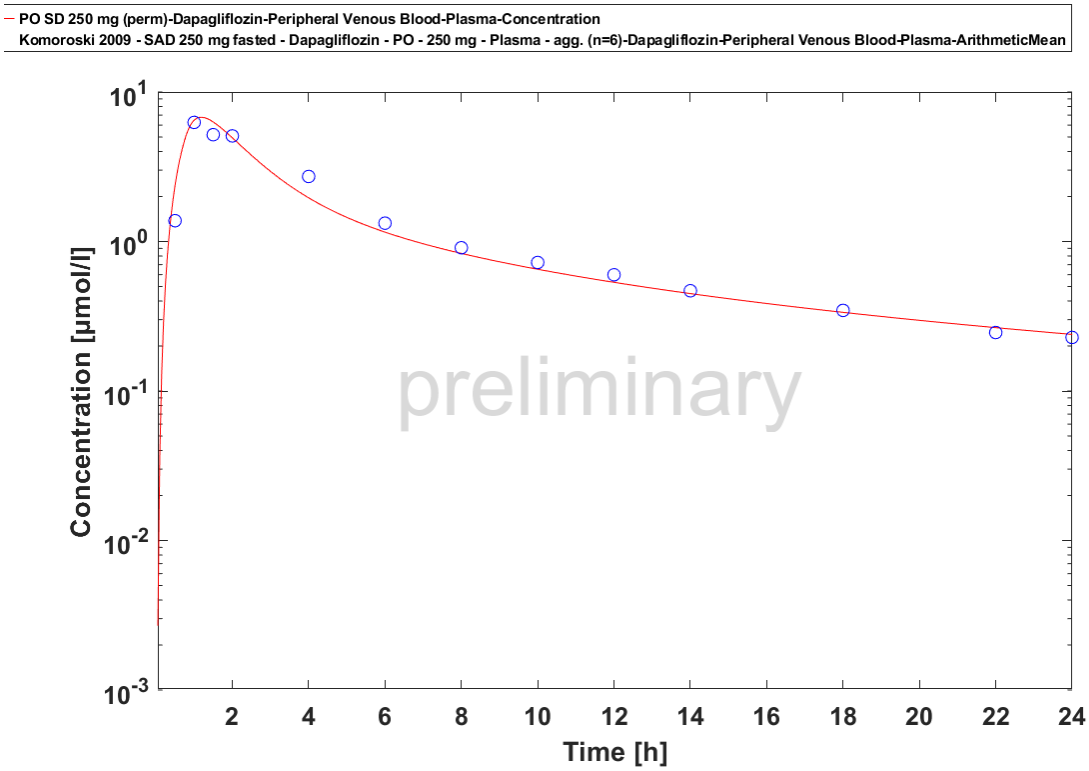
PO SD 100 mg (perm) (log)



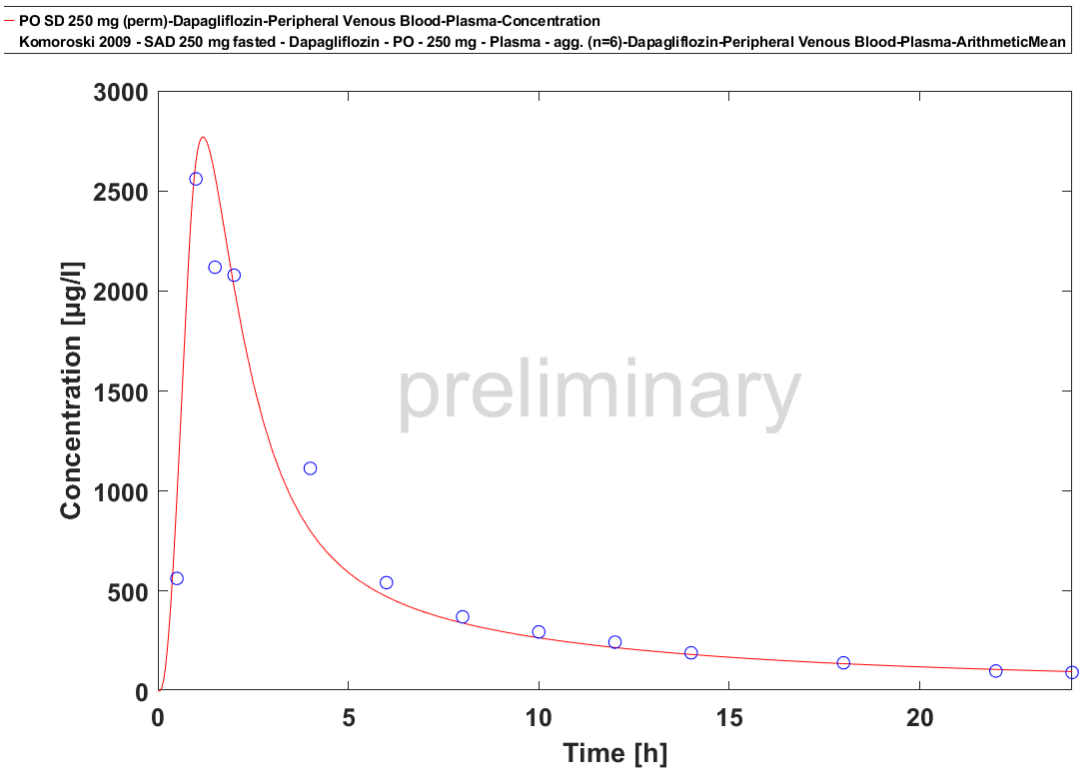
PO SD 100 mg (perm) (lin)



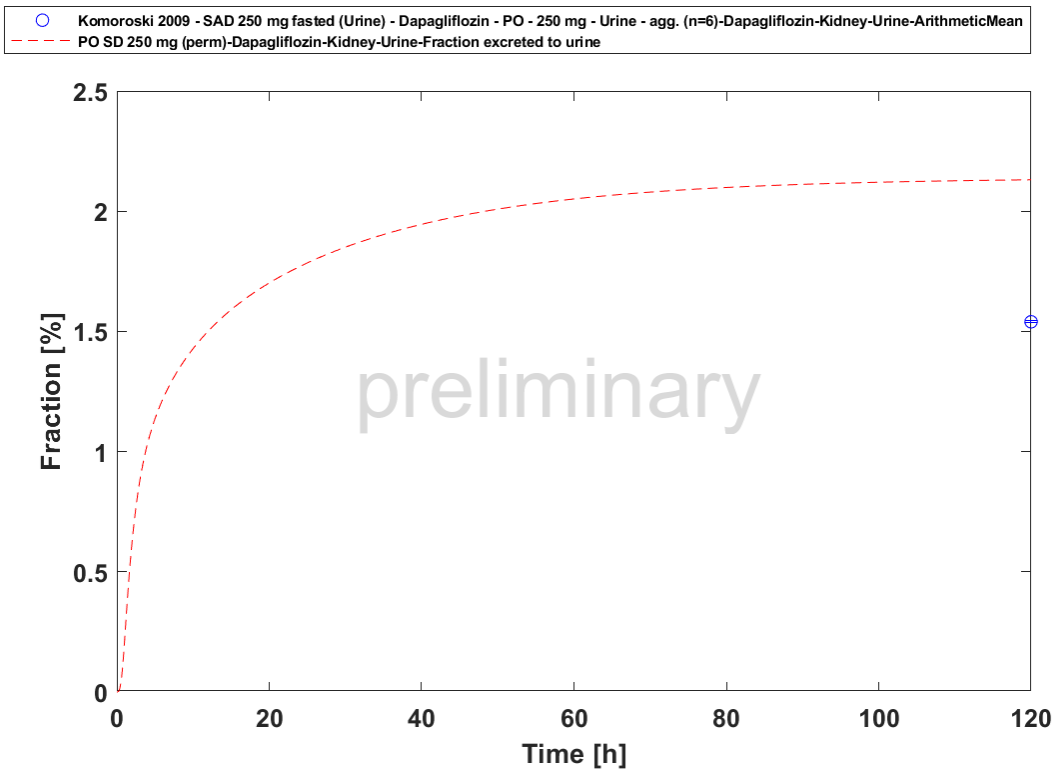
PO SD 100 mg (perm) (urinary excretion)



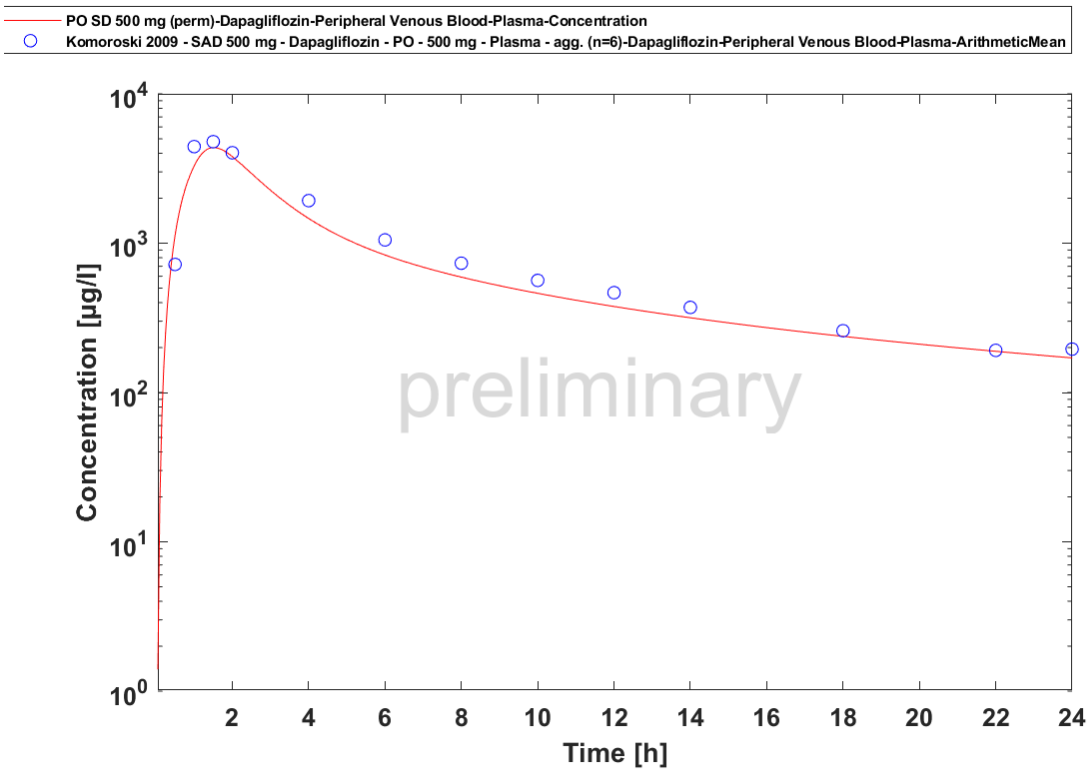
PO SD 250 mg (perm) (log)



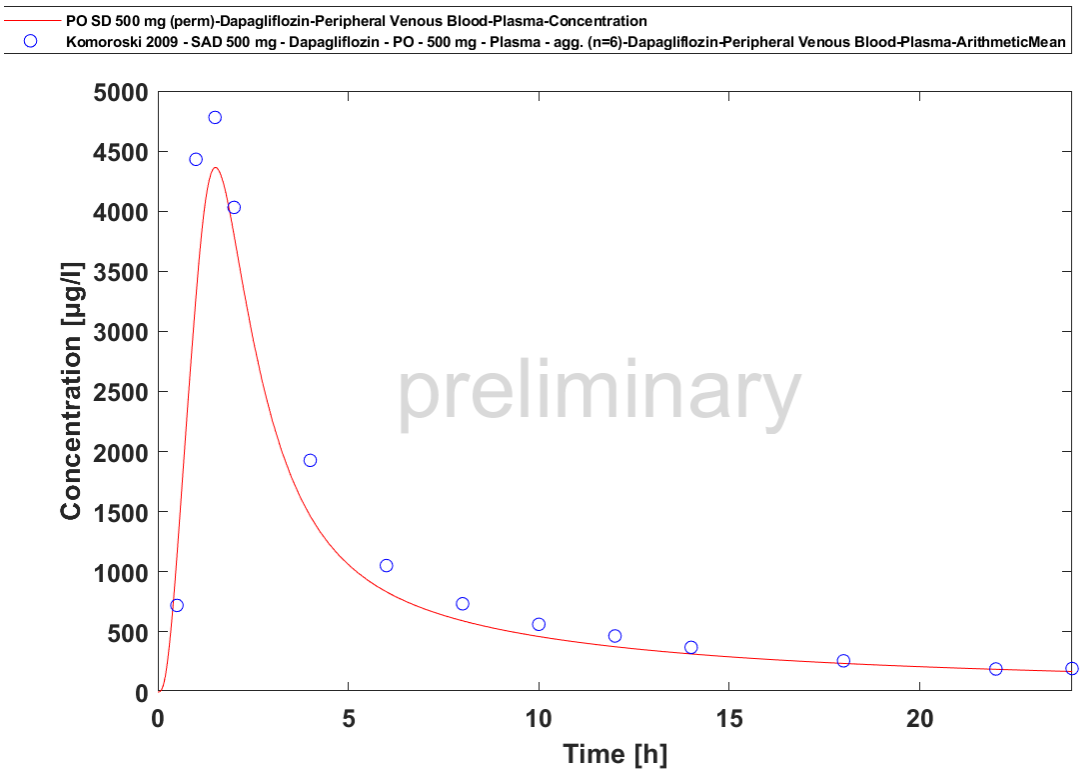
PO SD 250 mg (perm) (lin)



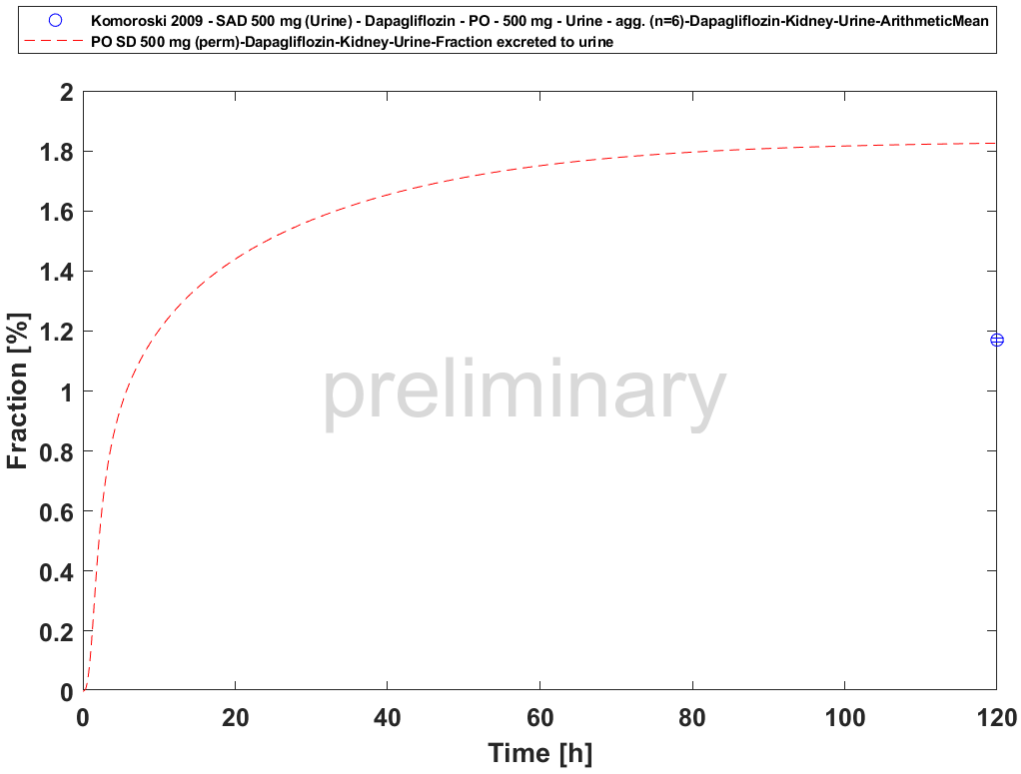
PO SD 250 mg (perm) (urinary excretion)



PO SD 500 mg (perm) (log)

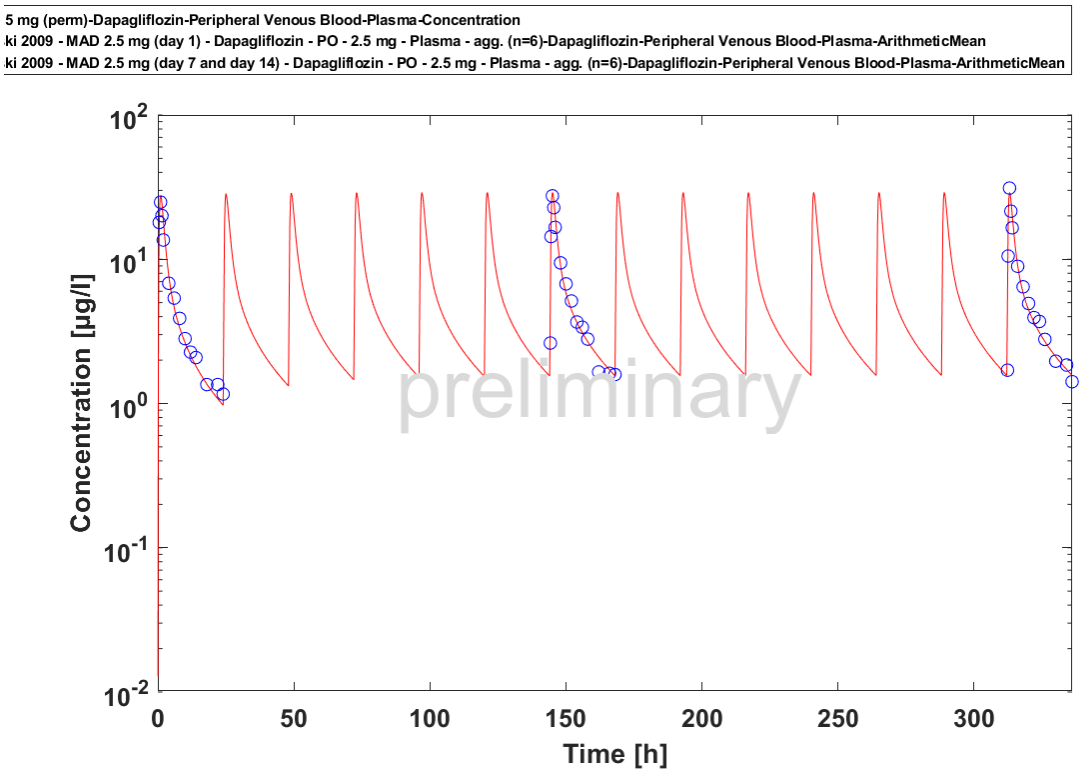


PO SD 500 mg (perm) (lin)

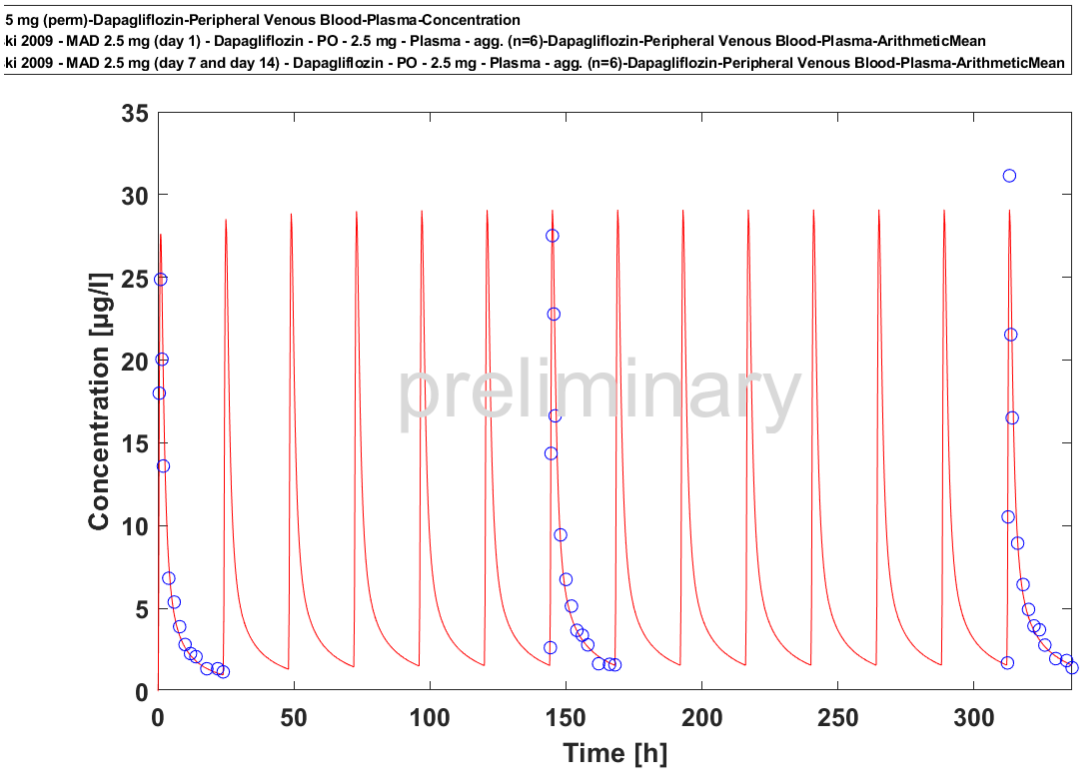


PO SD 500 mg (perm) (urinary excretion)

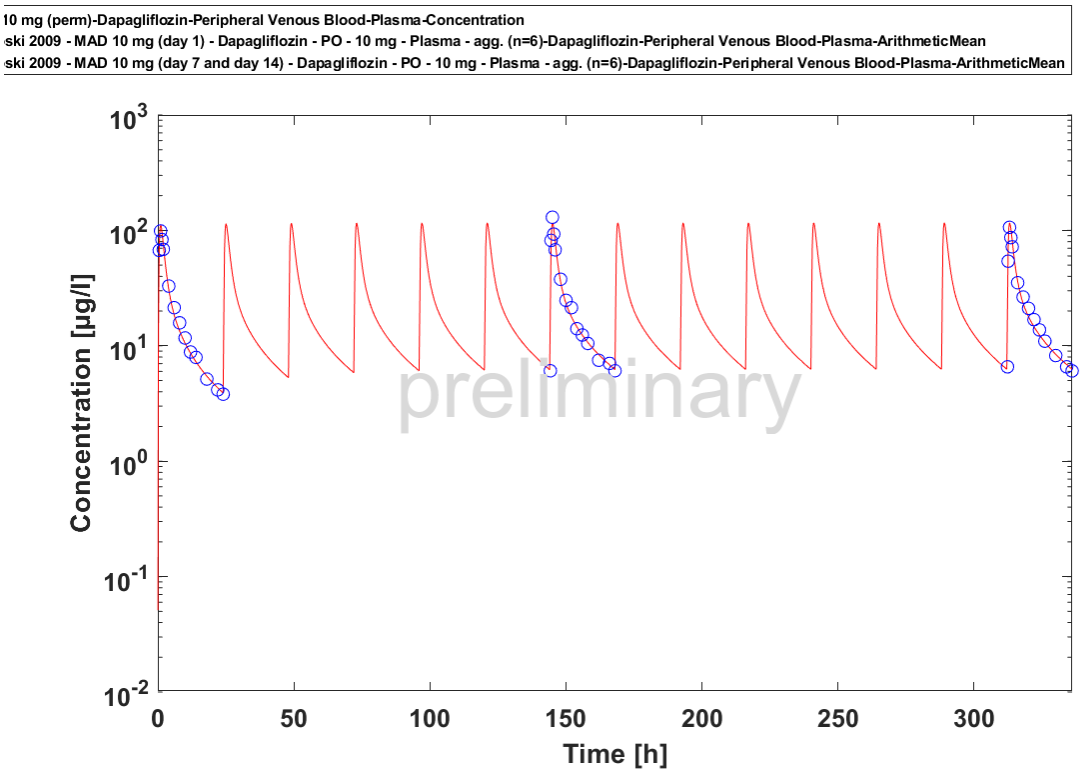
3.3.2 Model Verification



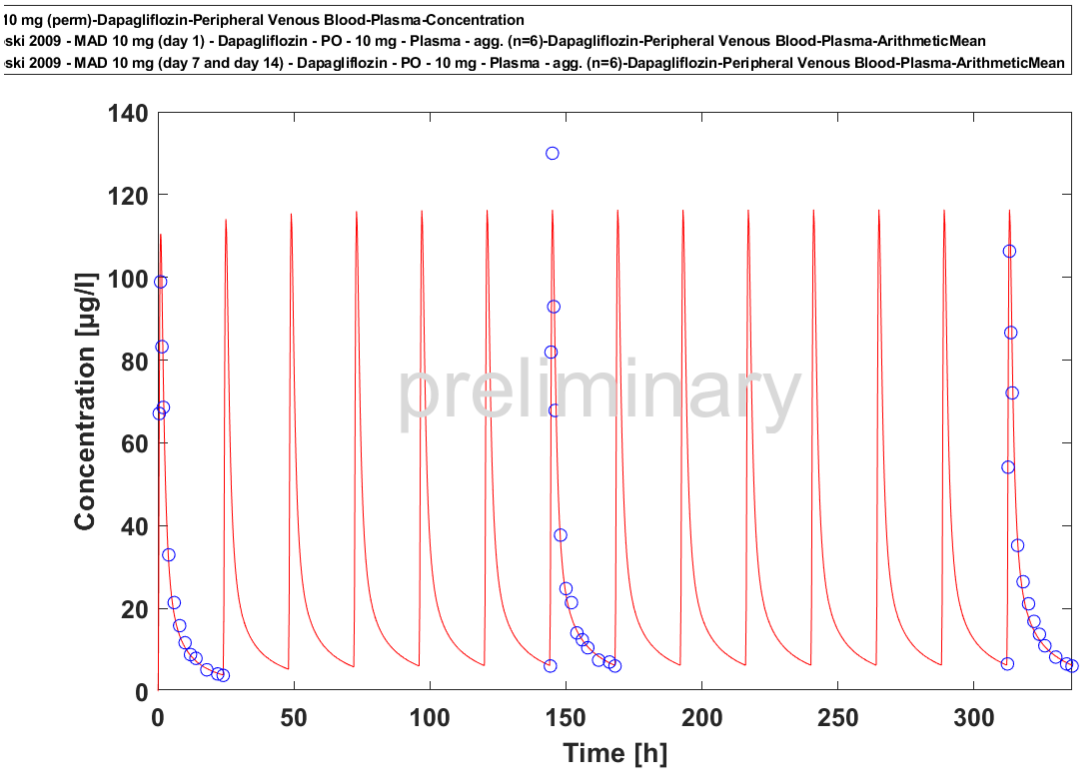
PO MD 2.5 mg (perm) (log)



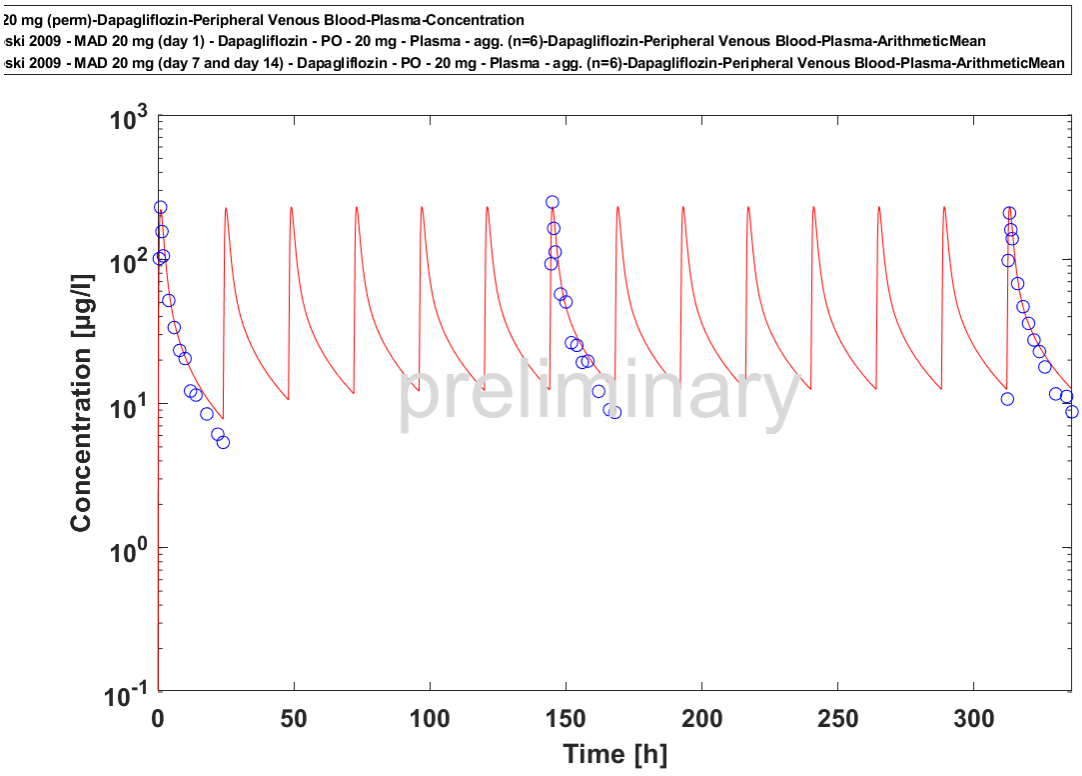
PO MD 2.5 mg (perm) (lin)



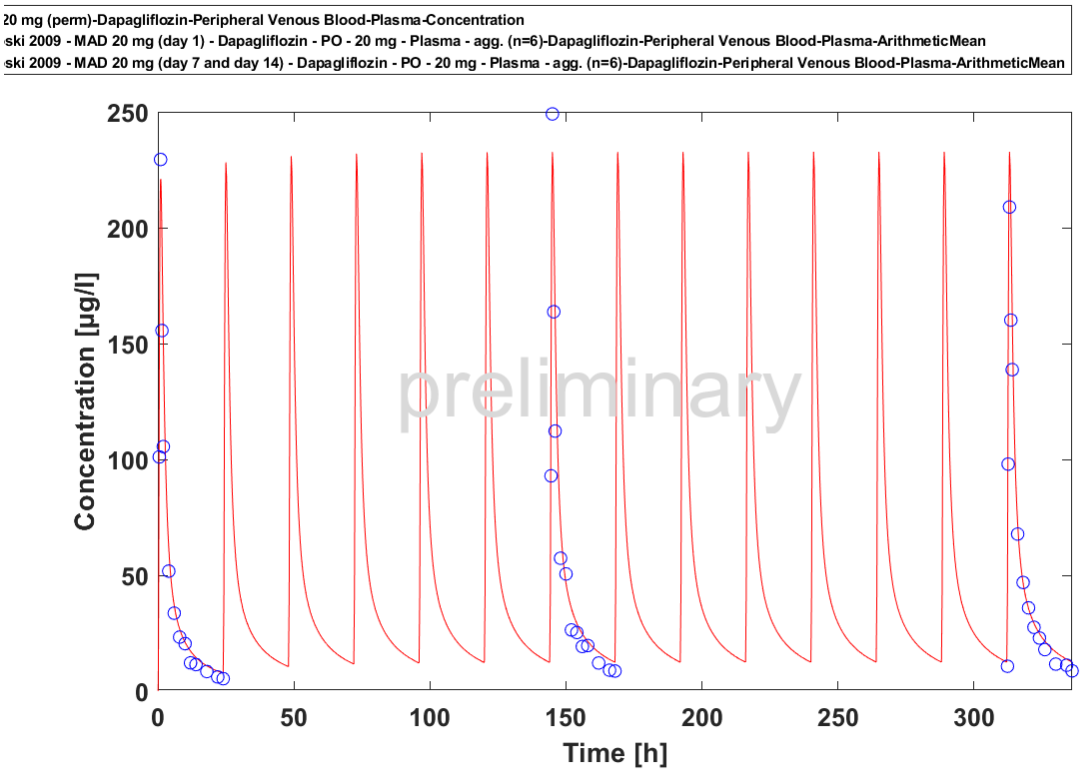
PO MD 10 mg (perm) (log)



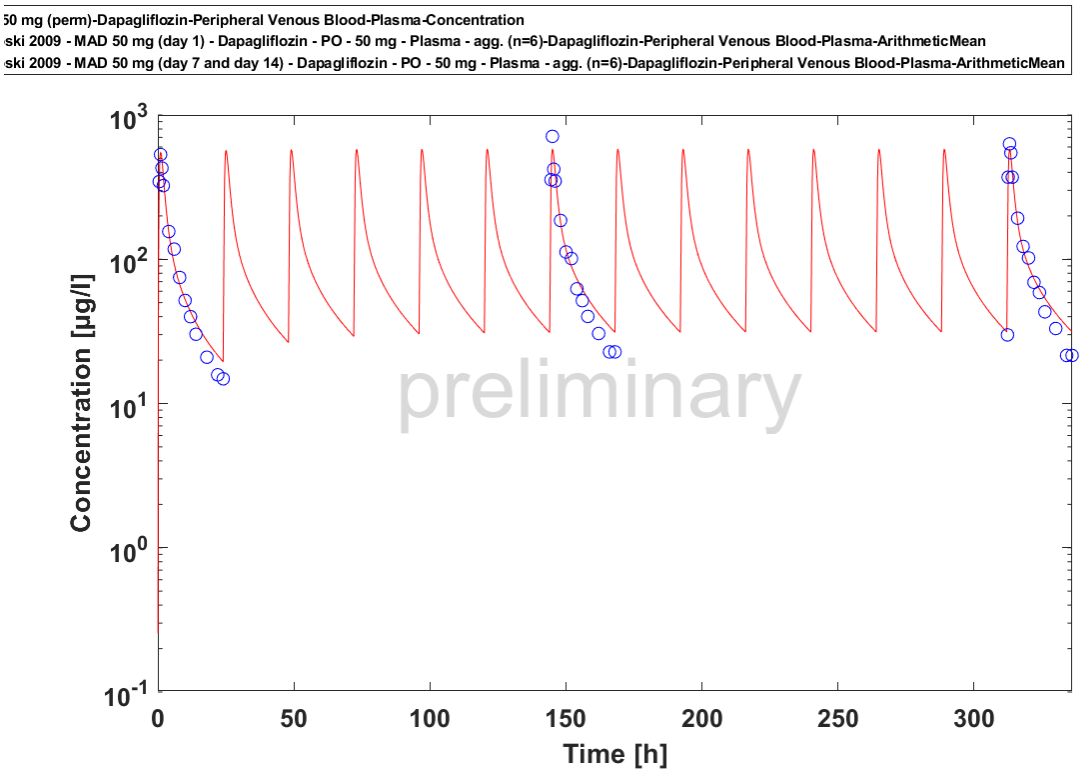
PO MD 10 mg (perm) (lin)



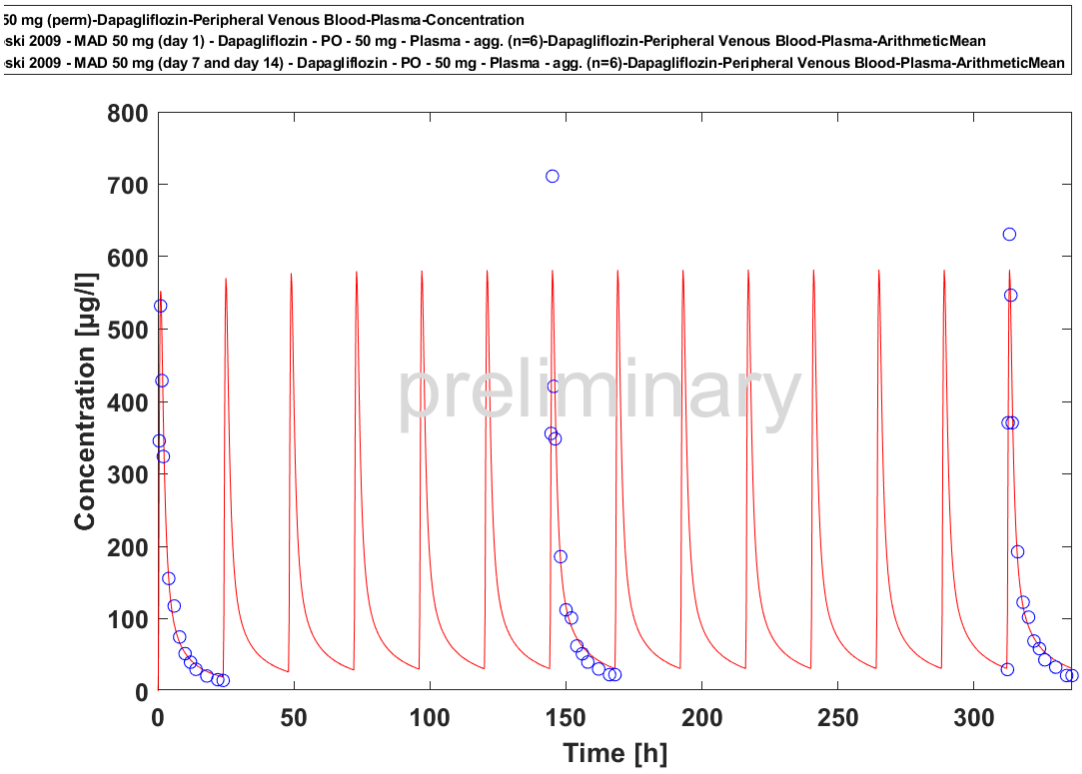
PO MD 20 mg (perm) (log)



PO MD 20 mg (perm) (lin)



PO MD 50 mg (perm) (log)



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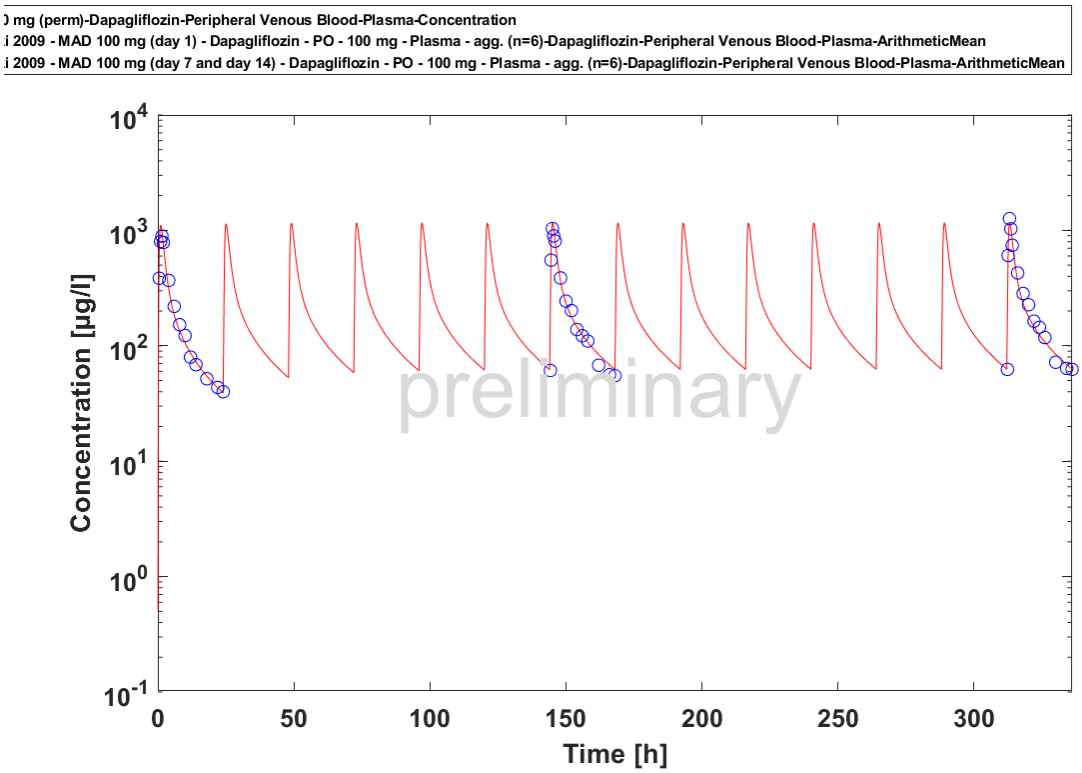
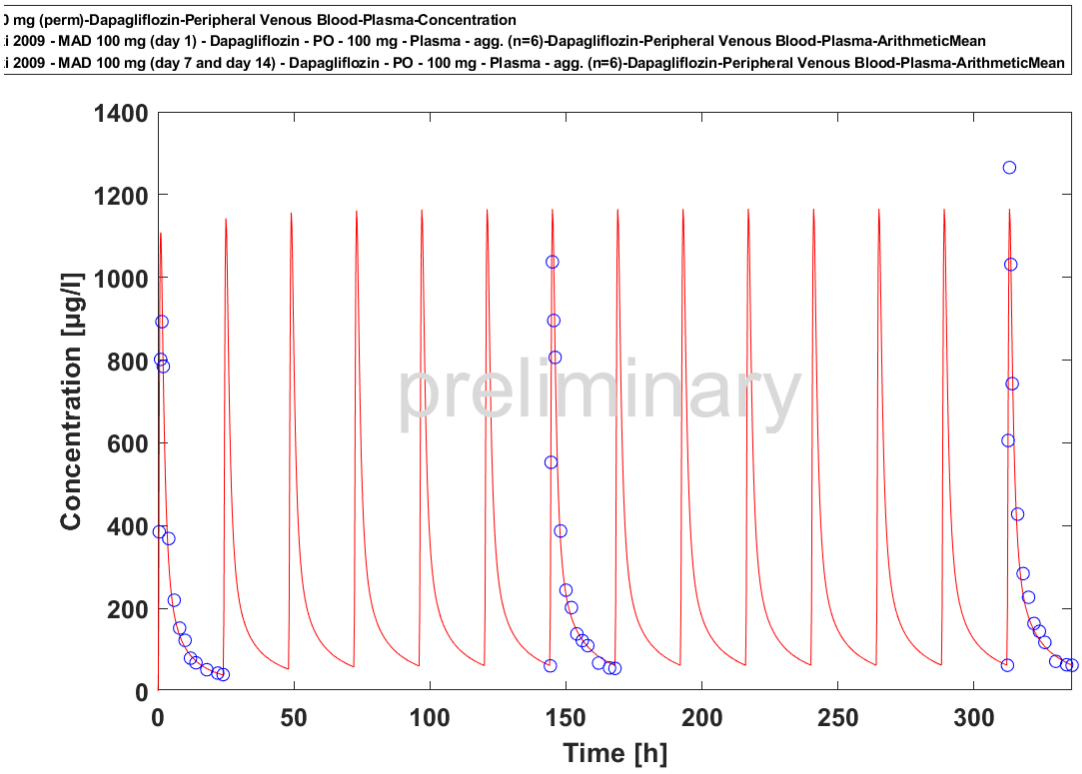
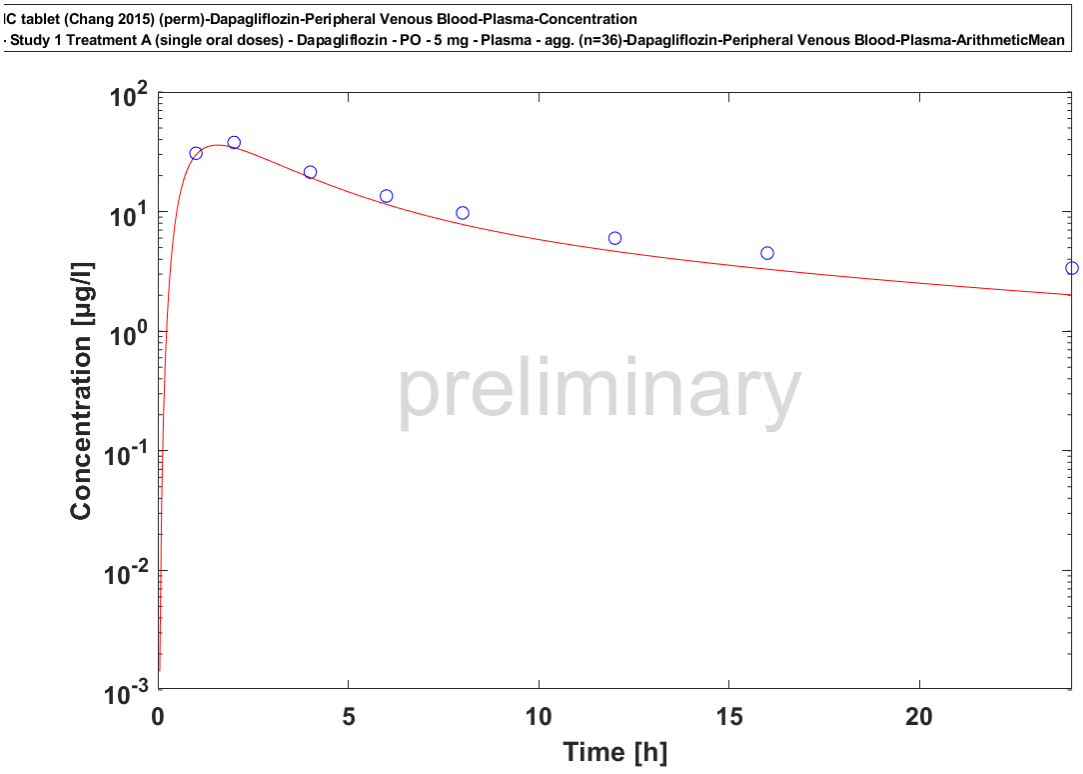


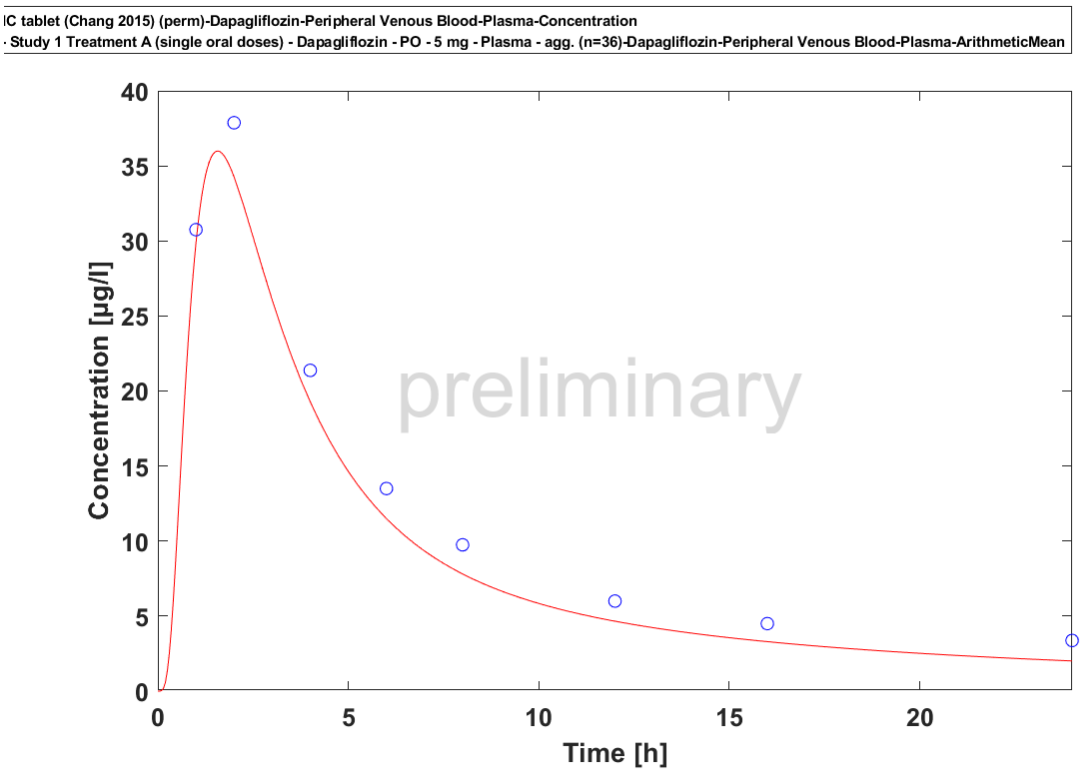
PO MD 100 mg (perm) (log)



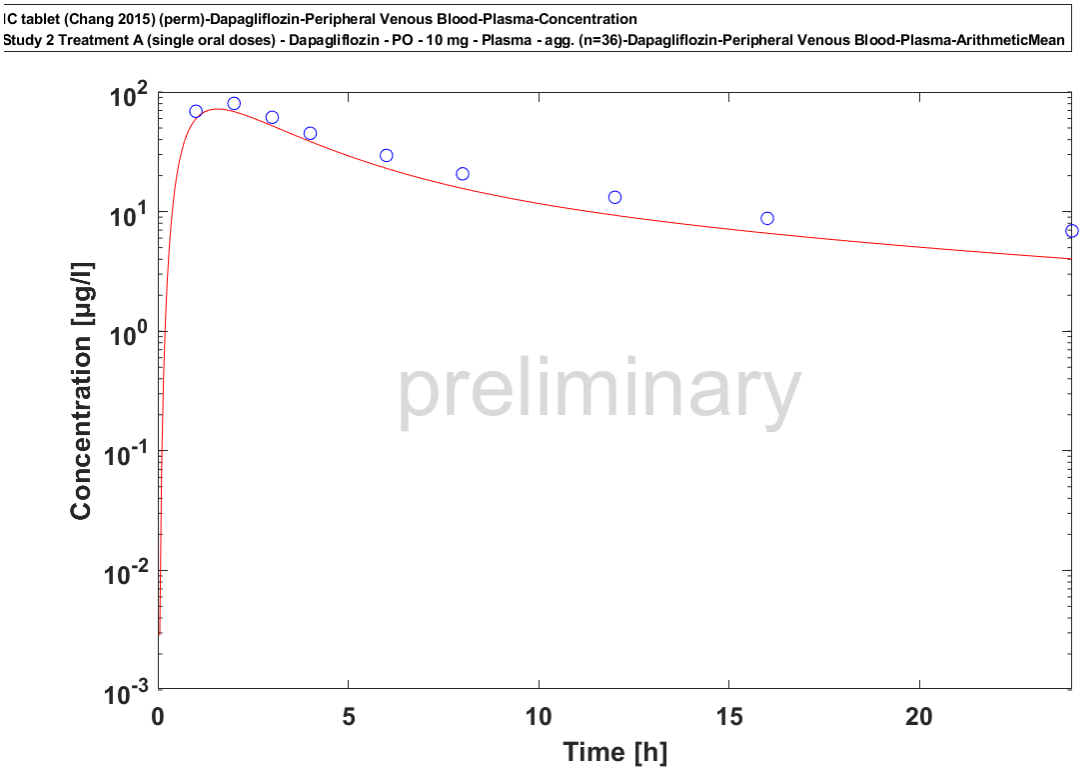
PO MD 100 mg (perm) (lin)



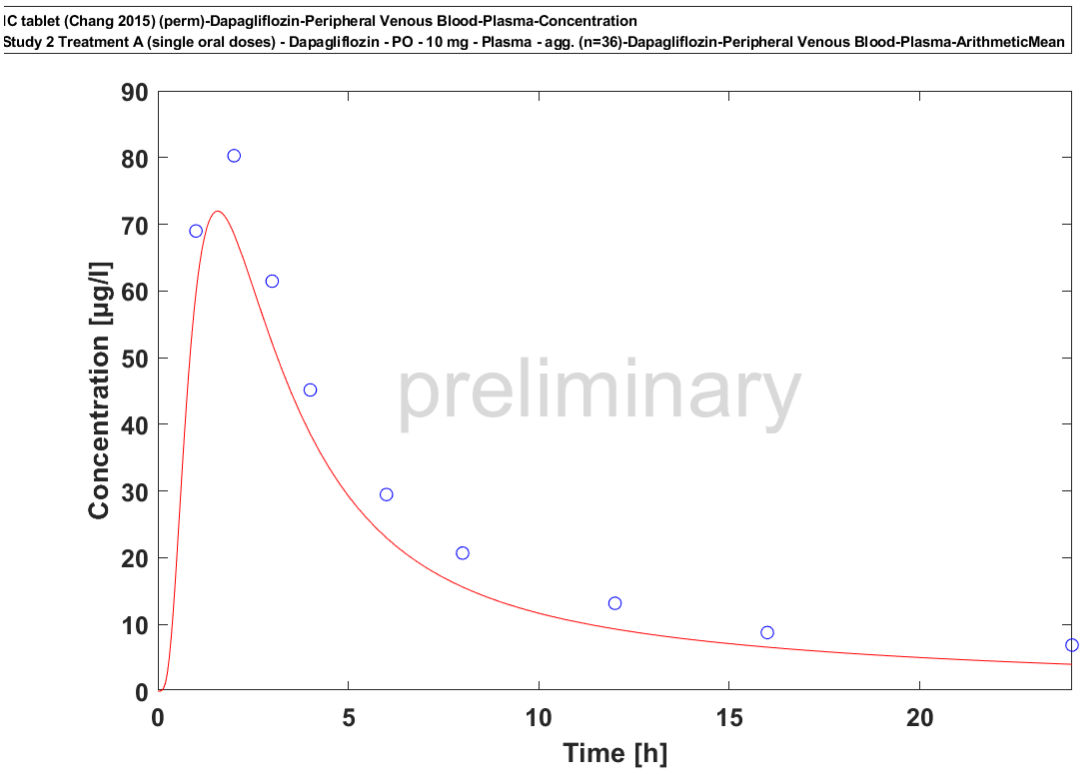
PO SD 5 mg IR tablet (perm) (log)



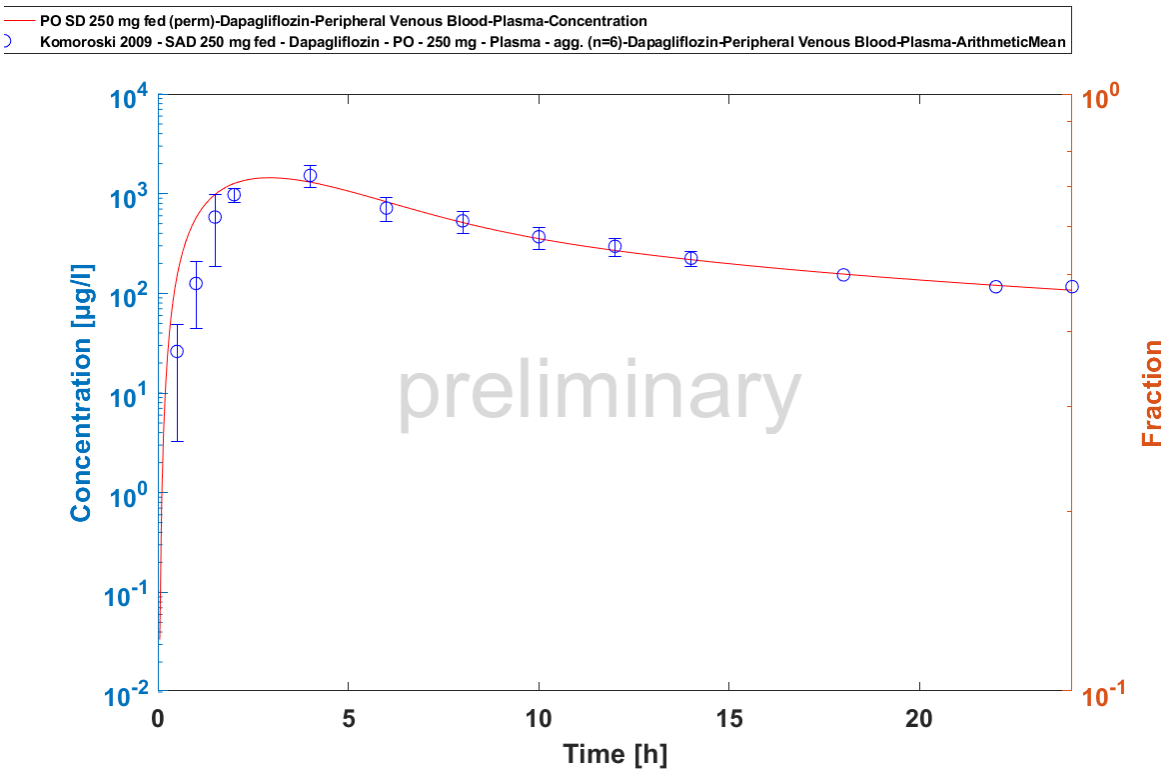
PO SD 5 mg IR tablet (perm) (lin)



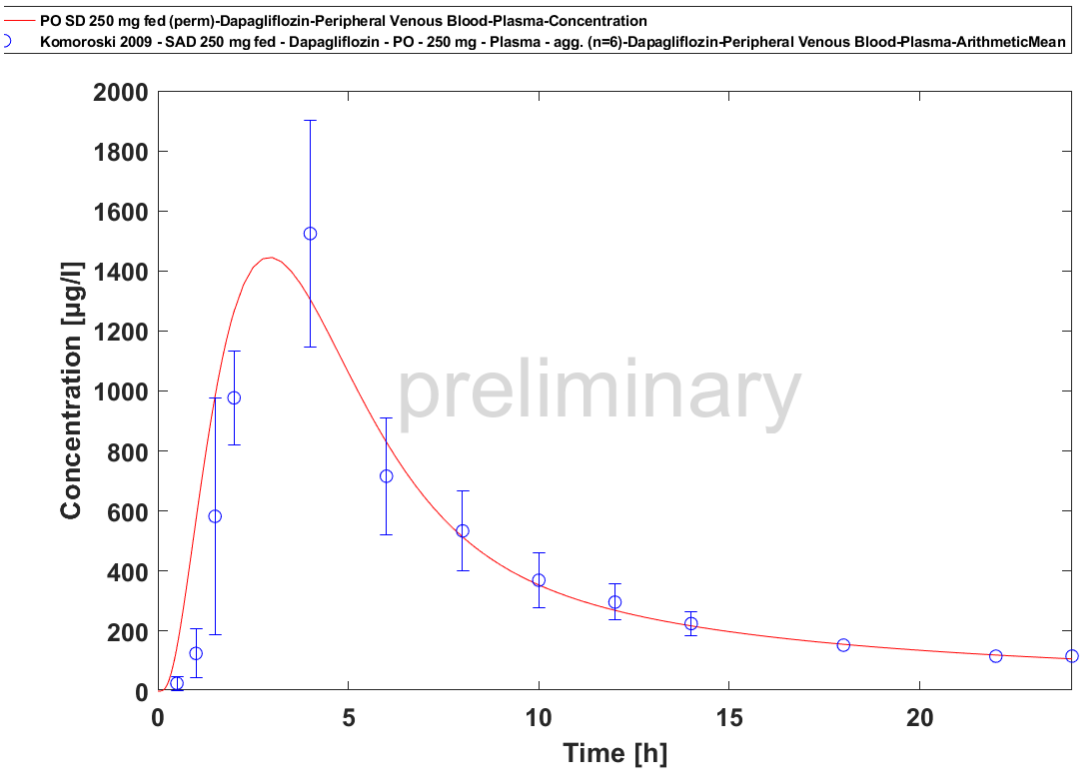
PO SD 10 mg IR tablet (perm) (log)



PO SD 10 mg IR tablet (perm) (lin)



PO SD 250 mg fed (perm) (log)



PO SD 250 mg fed (perm) (lin)

4 Conclusion

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

In particular, it applies quantitative metabolism by UGT1A9 and UGT2B7. Thus, the model is fit for purpose to be applied for the investigation of drug-drug interactions with regard to its UGT metabolism.

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