

Building and Evaluation of a PBPK Model for Fluvoxamine in Adults

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1 Introduction

Fluvoxamine is a selective serotonin reuptake inhibitor used to treat major depression and obsessive compulsive disorder ([Perucca 1994](#), [ANI Pharmaceuticals Inc. 2008](#)). Recommended doses are 50 to 300 mg once daily. The pharmacokinetics of orally administered single doses are linear. Following multiple oral administration, the pharmacokinetics at steady-state become non-linear, due to saturable Michaelis-Menten kinetics of the metabolic pathways ([Spigset 1998](#)). Metabolism of fluvoxamine includes hydroxylation via CYP1A2 and O-demethylation via the very polymorphic CYP2D6 ([Miura 2007](#), [Spigset 2001](#)). Following oral administration fluvoxamine is excreted via the urine as metabolites ([DeBree 1983](#)). The U.S. Food and Drug Administration (FDA) recommends fluvoxamine as strong clinical CYP1A2 and CYP2C19 index inhibitor to evaluate the impact of CYP1A2/CYP2C19 inhibition on CYP1A2/CYP2C19 substrates ([FDA 2017](#)). Furthermore, the FDA lists fluvoxamine as moderate CYP3A4 inhibitor.

The aim of this project was to develop a PBPK model of fluvoxamine, mechanistically describing its metabolism by CYP1A2 and CYP2D6 and its inhibitory effect on CYP1A2 and CYP3A4, that can be used for drug-drug interaction (DDI) predictions.

The presented model was developed and evaluated by Britz et al. ([Britz 2019](#))

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 PBPK model was built based on healthy individuals, using the reported mean values for age, weight, height, and genetic background for each study protocol. If no information on these parameters could be found, a healthy male European individual, 30 years of age, with a body weight of 73 kg and a height of 176 cm was used. To model the specific metabolic clearance, CYP1A2 and CYP2D6 were implemented in accordance with literature, using the PK-Sim expression database RT-PCR profiles ([Meyer 2012](#)) to define their relative expression in the different organs of the body. Glomerular filtration and enterohepatic cycling were enabled, as they are 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:

- single and multiple dose studies
- the effect of smoking on CYP1A2 metabolism of fluvoxamine
- plasma levels of fluvoxamine in CYP2D6 extensive (EM) and poor metabolizers (PM).

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

Parameter	Unit	Value	Source	Description
MW	g/mol	318.34	Drugbank	Molecular weight
pK _a		9.40 (base)	Hallifax 2007	Acid dissociation constant
Solubility (pH)	mg/mL	14.66 (7.0)	MSDS	Solubility
logP		2.80, 2.89, 3.20	Drugbank	Partition coefficient between octanol and water
fu	%	23.00	Claassen 1983	Fraction unbound in plasma
CYP2D6 K _m	μmol/L	76.30	Miura 2007	Michaelis-Menten constant
CYP2D6 k _{cat}	1/min	0	Crews 2014	Renal plasma clearance
CYP1A2 K _{ic} (competitive inhibition)	nmol/L	10.00	Karjalainen 2008 , Yao 2001	Conc. for half-maximal inactivation
CYP1A2 K _{iu} (uncompetitive inhibition)	nmol/L	10.00	Karjalainen 2008 , Yao 2001	Maximum inactivation rate
CYP3A4 K _i	μmol/L	1.60	Yao 2001 , Olesen 2000	Conc. for half-maximal inhibition

2.2.2 Clinical Data

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

The fluvoxamine PBPK model was developed using 26 different clinical studies with pharmacokinetic (PK) blood sampling. These studies include 1 study of 30 mg fluvoxamine administered intravenously (iv) as a single-dose, and 25 studies of fluvoxamine administered orally (po) in single- or multiple-doses. In the single-dose (s.d.) po studies fluvoxamine was administered in doses of 25 - 200 mg. In the multiple-dose po studies fluvoxamine was administered once (q.d.) or twice daily (b.i.d.), in doses of 10 - 150 mg per administration.

2.2.2.1 Model Building

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

Publication	Arm / Treatment / Information used for model building
Japanese Society 2015	Healthy Japanese adults with 30 mg as 60 min infusion or oral administration of 200 mg
de Vries 1993	Healthy adults with oral administration of 25-100 mg
Orlando 2010	Healthy adults with oral administration of 50 mg
Labellarte 2004	Healthy CYP2D6 EM with oral administration of 50 mg twice a day
Spigset 1998	Healthy CYP2D6 EM (80%) and PM (20%) with oral administration of doses between 12.5-100 mg twice a day
Fleishaker 1994	Healthy adults with oral administration of 50 mg or 100 mg once daily

2.2.2.2 Model Verification

The following studies were used for model verification:

Publication	Arm / Treatment / Information used for model building
Christensen 2002	Healthy CYP2D6 EM with oral administration of 10 mg or 25 mg twice a day and healthy CYP2D6 PM with oral administration of 10 mg or 25 mg once daily
Fukasawa 2006	Healthy Japanese adults with single oral doses of 50 mg
Japanese Society 2015	Healthy Japanese adults with single oral doses of 25-100 mg
Kunii 2005	Healthy CYP2D6 EM with single oral doses of 50 mg
Spigset 1995	Healthy smokers or non-smokers with oral administration of 50 mg as single dose
Spigset 1997	Healthy CYP2D6 EM or PM with oral administration of 50 mg as single dose
van Harten 1991	Healthy adults with oral administration of 50 mg as single dose
de Vries 1992	Healthy adults with oral administration of 50 mg twice a day
Bahrami 2007	Healthy adults with oral administration of 100 mg as single dose
de Bree 1983	Healthy adults with oral administration of 100 mg as single dose

2.3 Model Parameters and Assumptions

2.3.1 Absorption

Since a rapid dissolution and absorption was assumed for tablet as well as capsule formulation, the drug formulation was implemented as solution.

The specific intestinal permeability was identified during parameter identification.

2.3.2 Distribution

It is described in literature that fluvoxamine is moderately bound to plasma proteins (77%). This value was implemented in PK-Sim. The protein binding partner was set to unknown.

An important parameter influencing the distribution of a compound is lipophilicity. To accurately describe the distribution of fluvoxamine, logP was optimized during parameter identification to match observed clinical data.

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 `Schmitt` and cellular permeability calculation by `PK-Sim Standard`.

The specific organ permeability was further optimized during parameter identification.

2.3.3 Metabolism and Elimination

The final model applies metabolism by CYP1A2, CYP2D6 and glomerular filtration. The metabolic processes by CYP1A2 and CYP2D6 were described by Michaelis-Menten kinetics. The Michaelis-Menten constant K_m for CYP2D6 metabolism was fixed according to literature values, other parameters were identified during parameter identification.

To distinguish between fluvoxamine metabolism in CYP2D6 extensive metabolizers and poor metabolizers, the CYP2D6 catalytic rate constant k_{cat} of PMs was set to zero. This assumption was made because CYP2D6 PMs were characterized by absent CYP2D6 enzymatic activity [Crews 2014](#), which results in a predicted 1.5-fold increase of the fluvoxamine AUC in CYP2D6 PMs compared with CYP2D6 EMs.

Smoking is the strongest known inducer of CYP1A2 and results in higher metabolism of CYP1A2 substrates [Zhou 2009](#). As no detailed information on the frequency, duration, and amount of smoking was available from literature, the induction of CYP1A2 was implemented as a static 1.38-fold increase in enzyme activity. This factor was optimized based on the study of Spigset et al. ([Spigset 1995](#)) resulting in a 39% reduction of the fluvoxamine AUC in smokers.

2.3.4 Automated Parameter Identification

This is the result of the final parameter identification.

Model Parameter	Optimized Value	Unit
logP	3.57	log units
CYP1A2 K_m	7.35	nmol/L
CYP1A2 k_{cat} (non-smokers)	0.016	1/min
CYP1A2 k_{cat} (smokers)	0.022	1/min
CYP2D6 k_{cat} (EM)	110.56	1/min
Specific intestinal permeability	2.74 E-6	dm/min

3 Results and Discussion

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

The model was evaluated covering data from studies including in particular

- intravenous and oral administration
- single and multiple doses
- a dose range from 25 mg to 200 mg
- CYP2D6 EM and PM

- smoker and non-smoker

The model quantifies metabolism via CYP1A2 and CYP2D6 and the effect of smoking and different CYP2D6 genotypes on fluvoxamine metabolism.

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: Fluvoxamine

Parameters

Name	Value	Value Origin	Alternative	Default	
Solubility at reference pH	14.66 mg/ml		Measurement	True	
Reference pH	7		Measurement	True	
Lipophilicity	3.5726507829 Log Units	Parameter Identification	Measurement	True	
Fraction unbound (plasma, reference value)	0.23	Publication- Claassen et al., Review of the animal pharmacology and pharmacokinetics of fluvoxamine. Br. J. Clin. Pharmacol. 15, 349S-355S (1983).	Measurement	True	
Specific intestinal permeability (transcellular)	2.7380788903E-06 dm/min	Parameter Identification	Fitted	True	
F	3				
Is small molecule	Yes				
Molecular weight	318.335 g/mol				
Plasma protein binding partner	Unknown				

Calculation methods

Name	Value	
Partition coefficients	Schmitt	
Cellular permeabilities	PK-Sim Standard	

Processes

Metabolizing Enzyme: CYP1A2-Fit

Molecule: CYP1A2

Parameters

Name	Value	Value Origin	
In vitro Vmax for liver microsomes	0 pmol/min/mg mic. protein		
Content of CYP proteins in liver microsomes	45 pmol/mg mic. protein	Unknown	
Km	0.0073460807948 $\mu\text{mol/l}$		
kcat	0.0155447966 1/min	Unknown	

Metabolizing Enzyme: CYP2D6-Miura2007

Molecule: CYP2D6

Parameters

Name	Value	Value Origin	
In vitro Vmax/recombinant enzyme	0.69 pmol/min/pmol rec. enzyme		
Km	76.3 $\mu\text{mol/l}$		
kcat	110.5561921693 1/min	Parameter Identification	

Systemic Process: Glomerular Filtration-4% Urine

Species: Human

Parameters

Name	Value	Value Origin	
GFR fraction	1		

Inhibition: CYP1A2-Karjalainen2008/Yao2001

Molecule: CYP1A2

Parameters

Name	Value	Value Origin	
Ki_c	10 nmol/l	Publication-In Vitro-Karjalainen et al. In vitro inhibition of CYP1A2 by model inhibitors, anti-inflammatory analgesics and female sex steroids: predictability of in vivo interactions. Basic Clin. Pharmacol. Toxicol. 103, 157–65 (2008) and Yao, C. et al. Fluvoxamine-theophylline interaction: gap between in vitro and in vivo inhibition constants toward cytochrome P4501A2. Clin. Pharmacol. Ther. 70, 415–24 (2001)	

Name	Value	Value Origin	
Ki_u	10 nmol/l	Publication-In Vitro-Karjalainen et al. In vitro inhibition of CYP1A2 by model inhibitors, anti-inflammatory analgesics and female sex steroids: predictability of in vivo interactions. Basic Clin. Pharmacol. Toxicol. 103, 157–65 (2008) and Yao, C. et al. Fluvoxamine-theophylline interaction: gap between in vitro and in vivo inhibition constants toward cytochrome P4501A2. Clin. Pharmacol. Ther. 70, 415–24 (2001)	

Inhibition: CYP3A4-Olesen2000/Yao2001

Molecule: CYP3A4

Parameters

Name	Value	Value Origin	
Ki	1.6 μ mol/l	Publication-In Vitro-Olesen et al. Fluvoxamine-Clozapine drug interaction: inhibition in vitro of five cytochrome P450 isoforms involved in clozapine metabolism. J. Clin. Psychopharmacol. 20, 35–42 (2000) and Yao, C. et al. Fluvoxamine-theophylline interaction: gap between in vitro and in vivo inhibition constants toward cytochrome P4501A2. Clin. Pharmacol. Ther. 70, 415–24 (2001)	

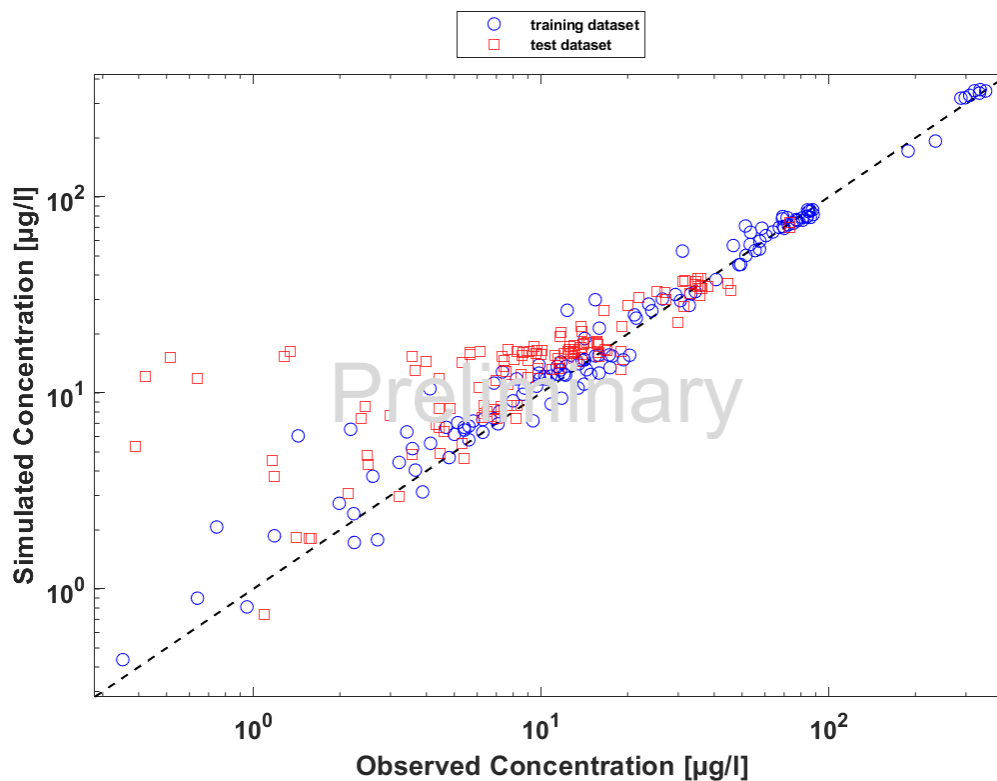
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Type: Dissolved

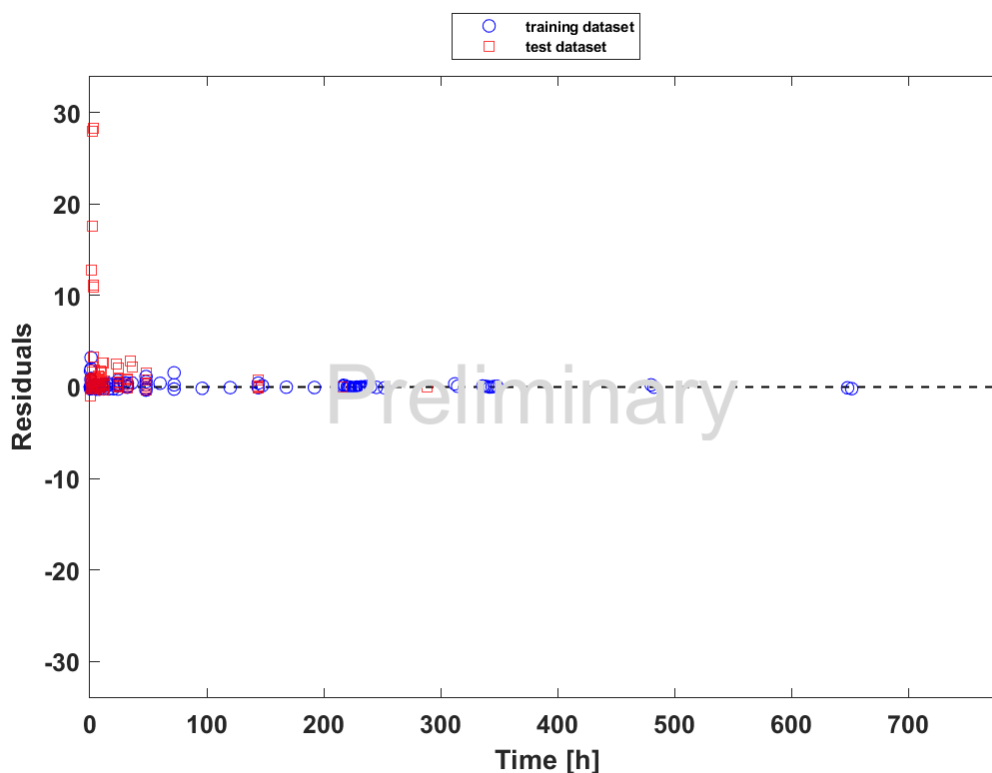
3.2 Diagnostics Plots

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



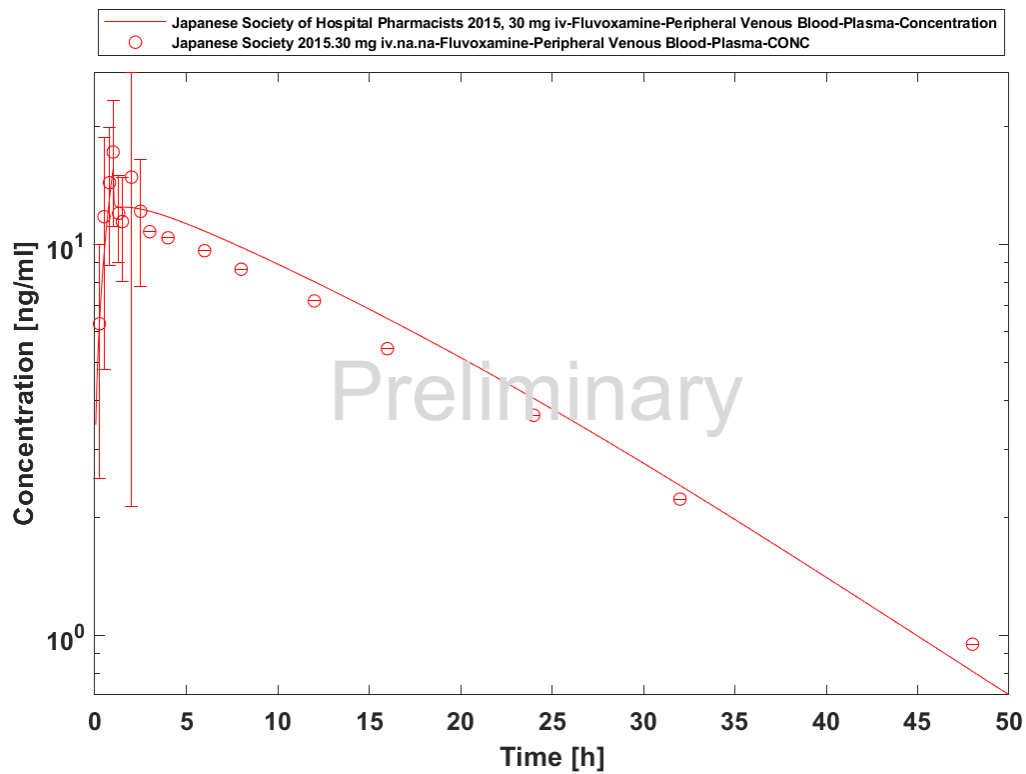
Goodness of fit plot for concentration in plasma

GMFE = 1.398262

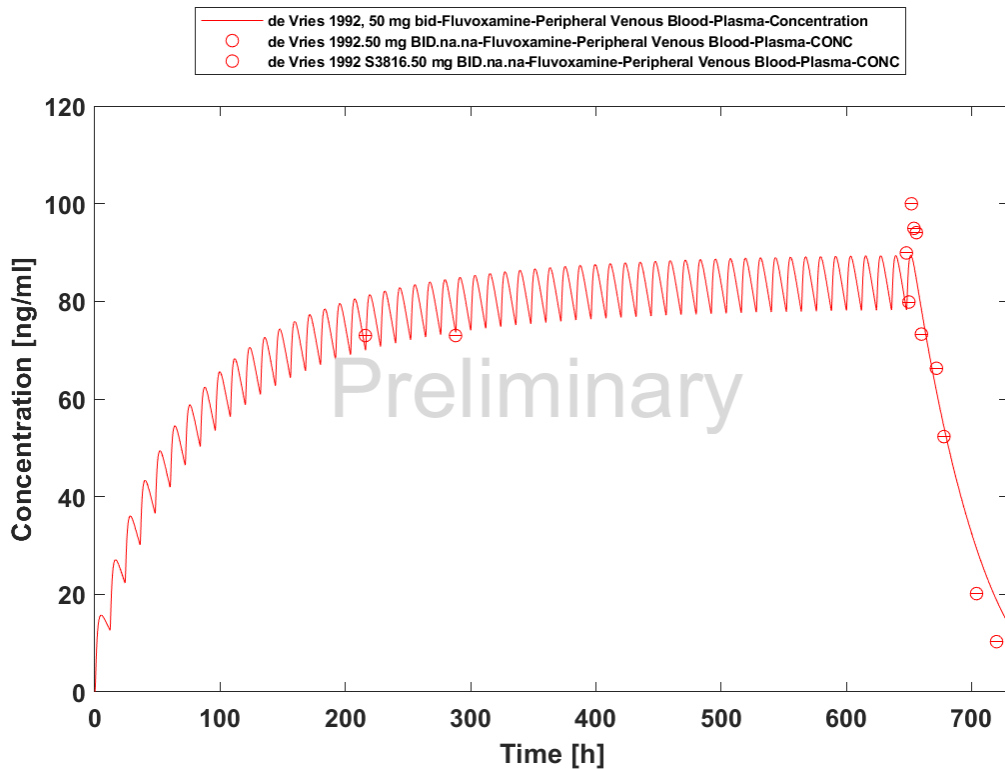
3.3 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in [Section 2.2.2](#) are presented below.

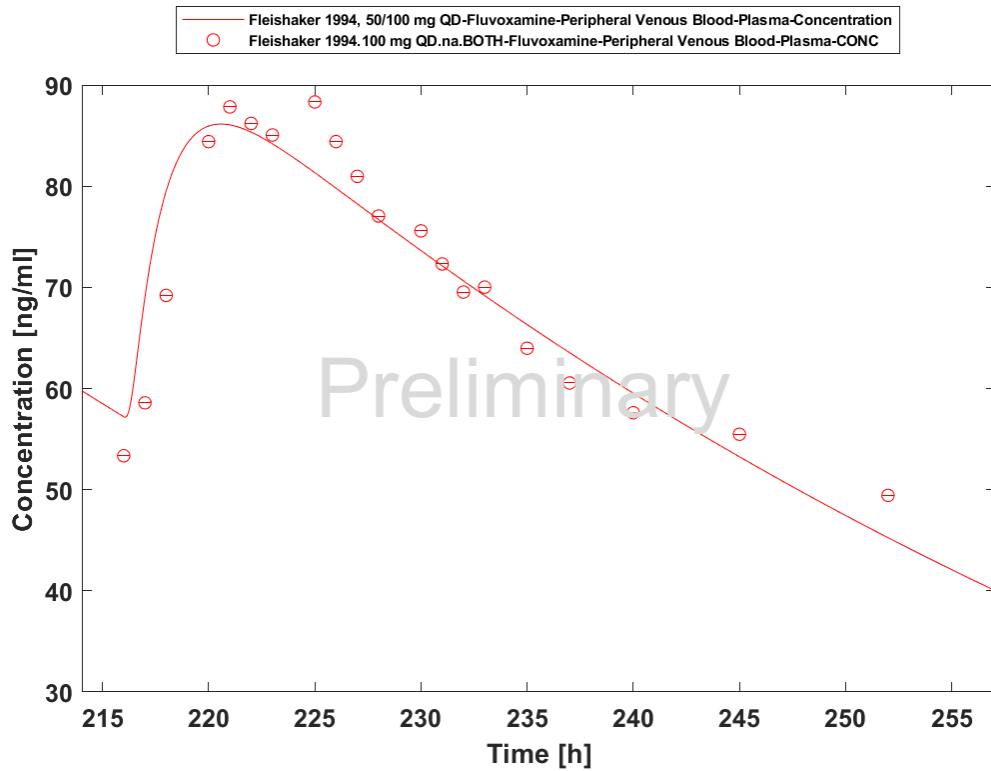
3.3.1 Model Building



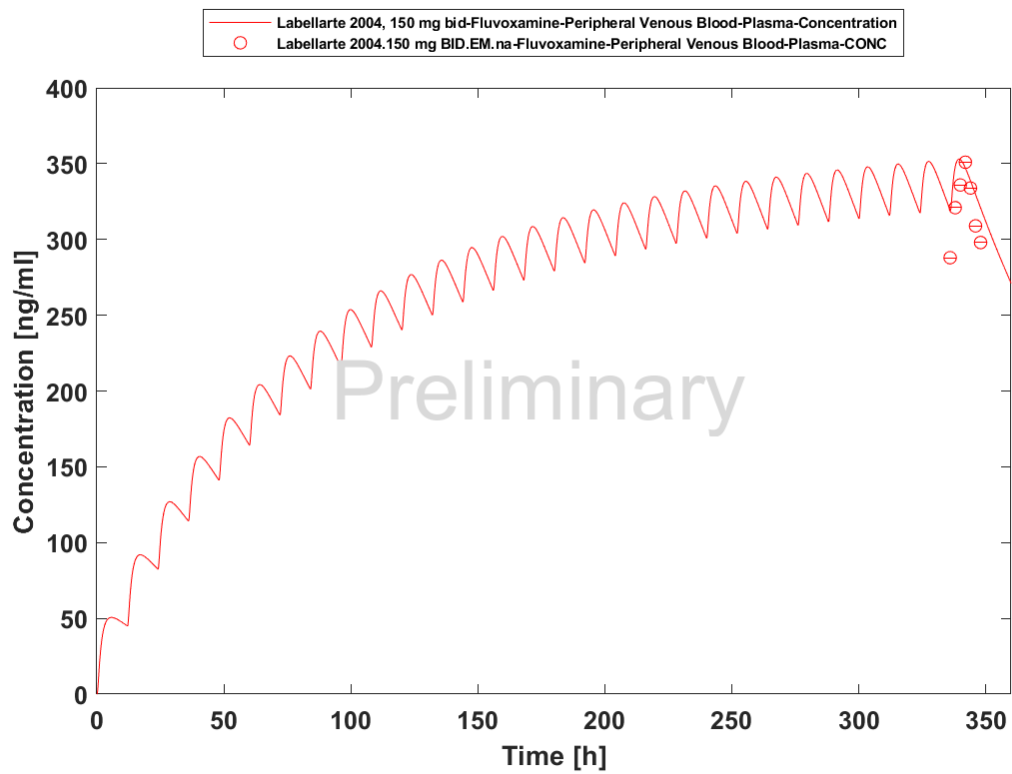
Time Profile Analysis



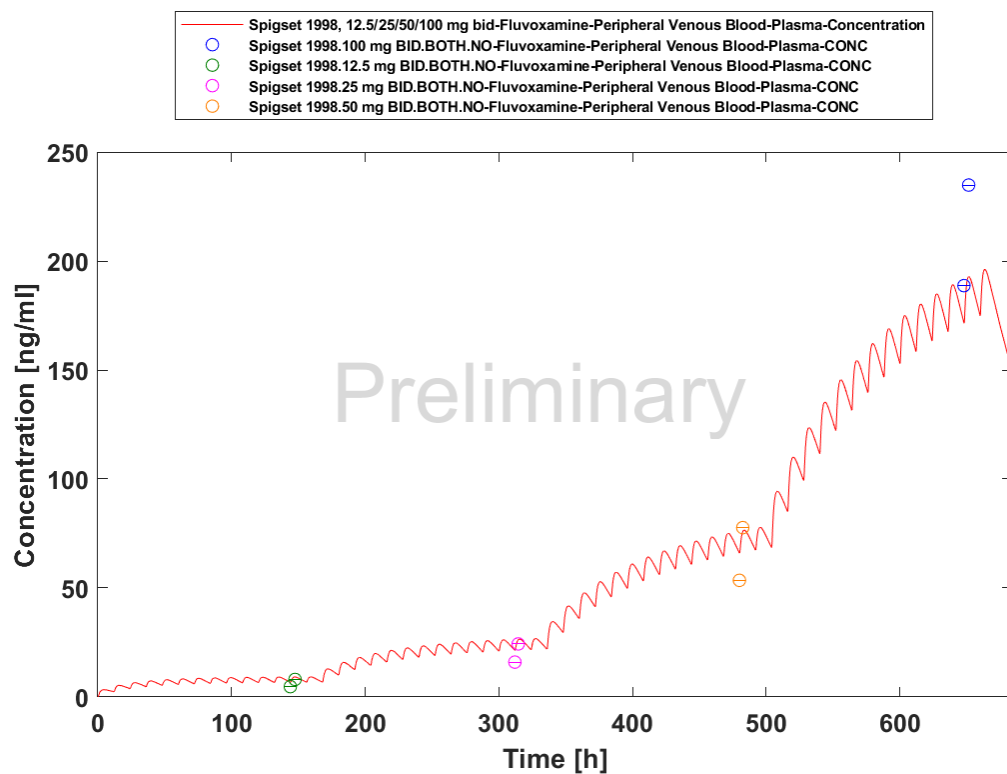
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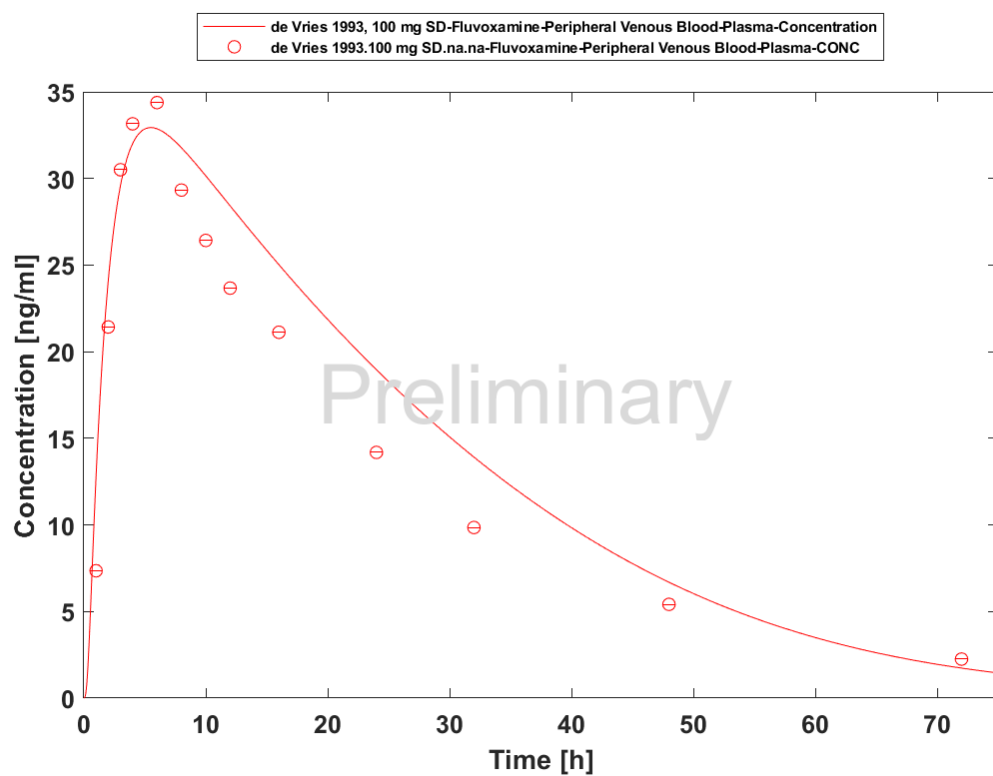
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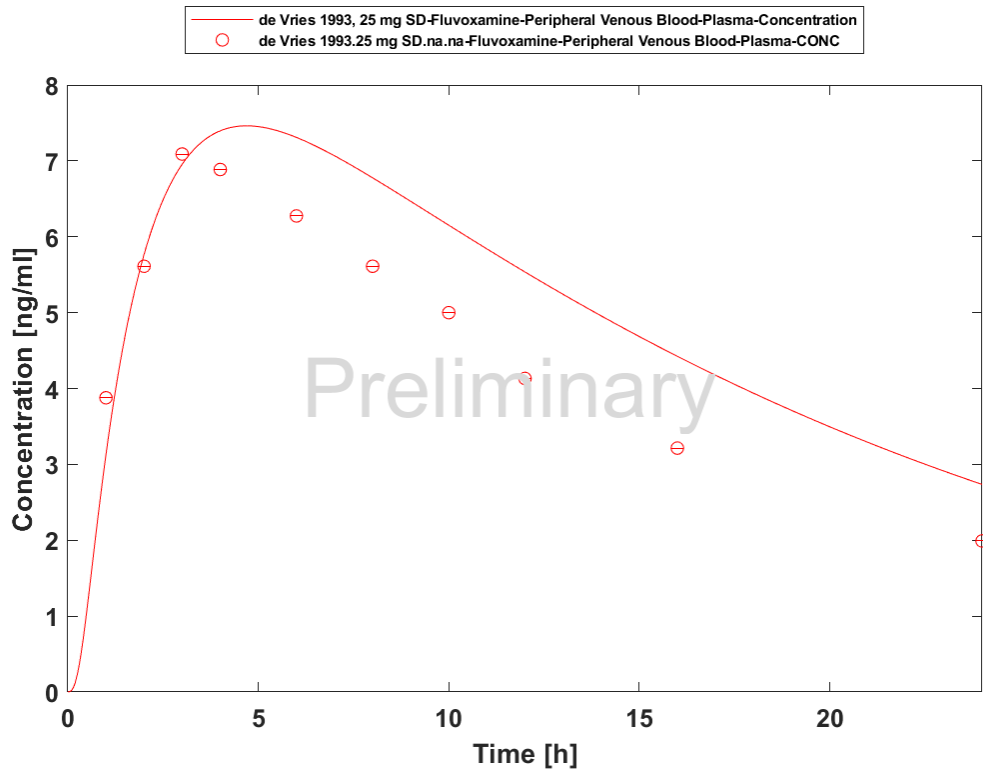
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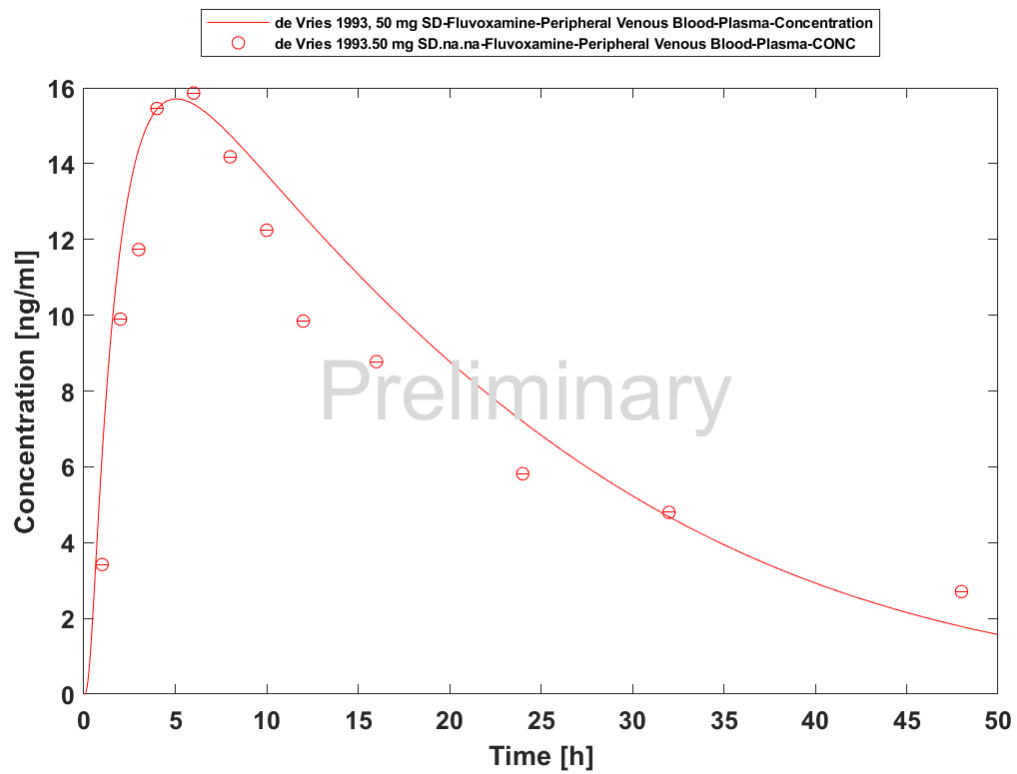
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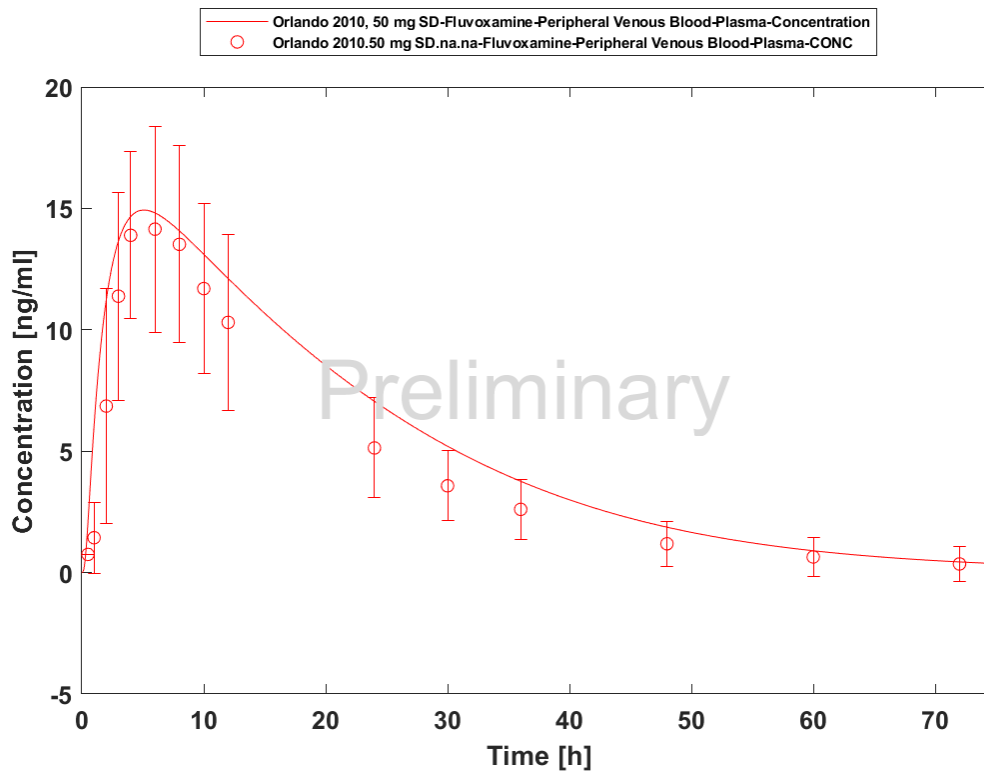
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Time Profile Analysis

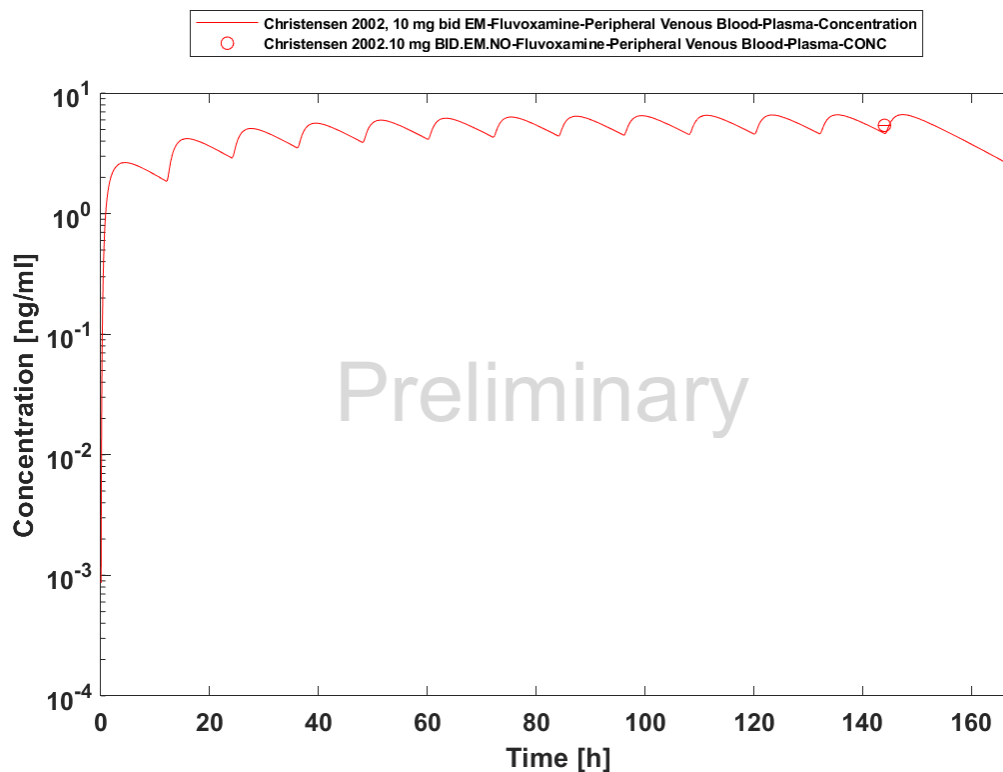


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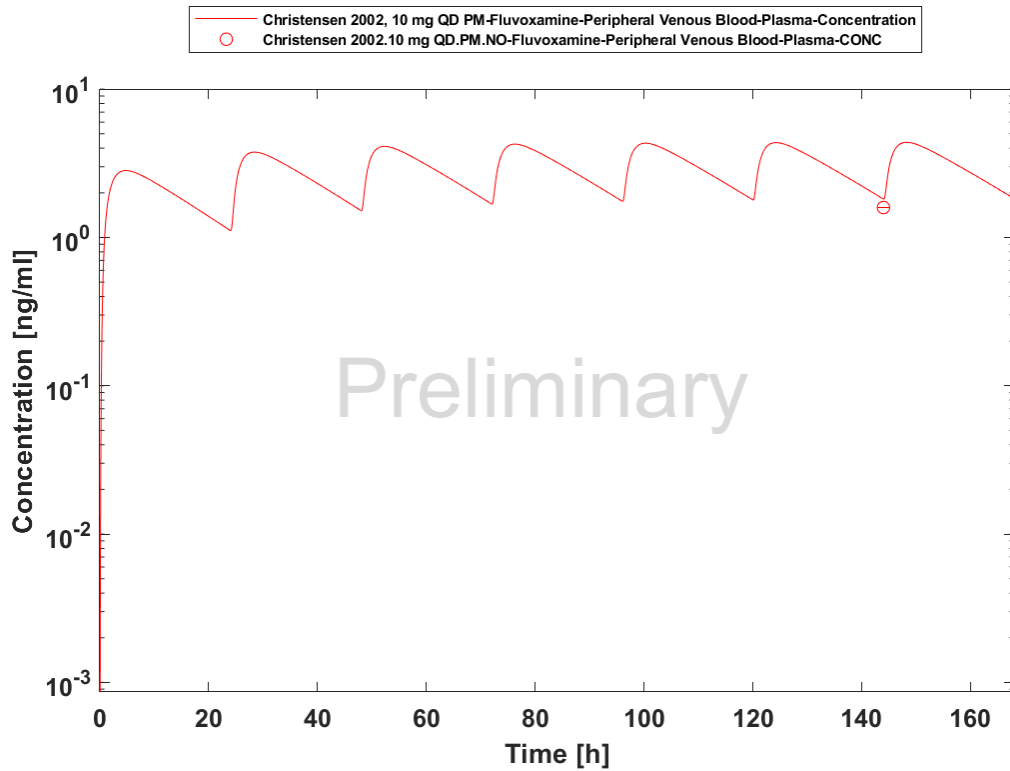


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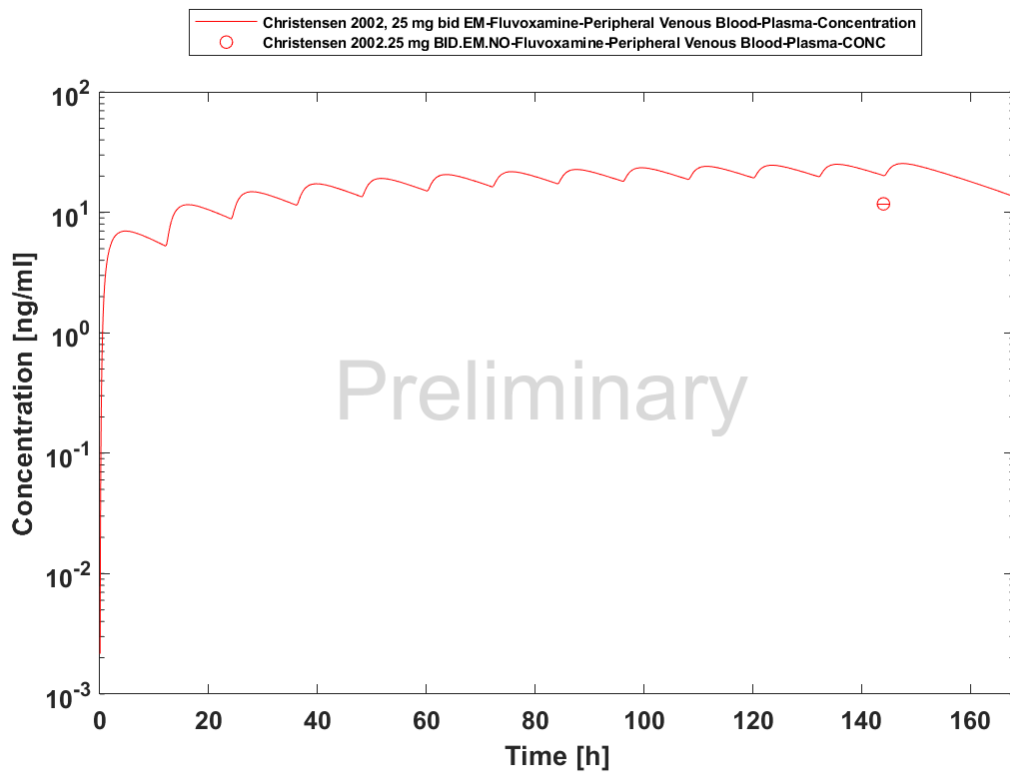
3.3.2 Model Verification



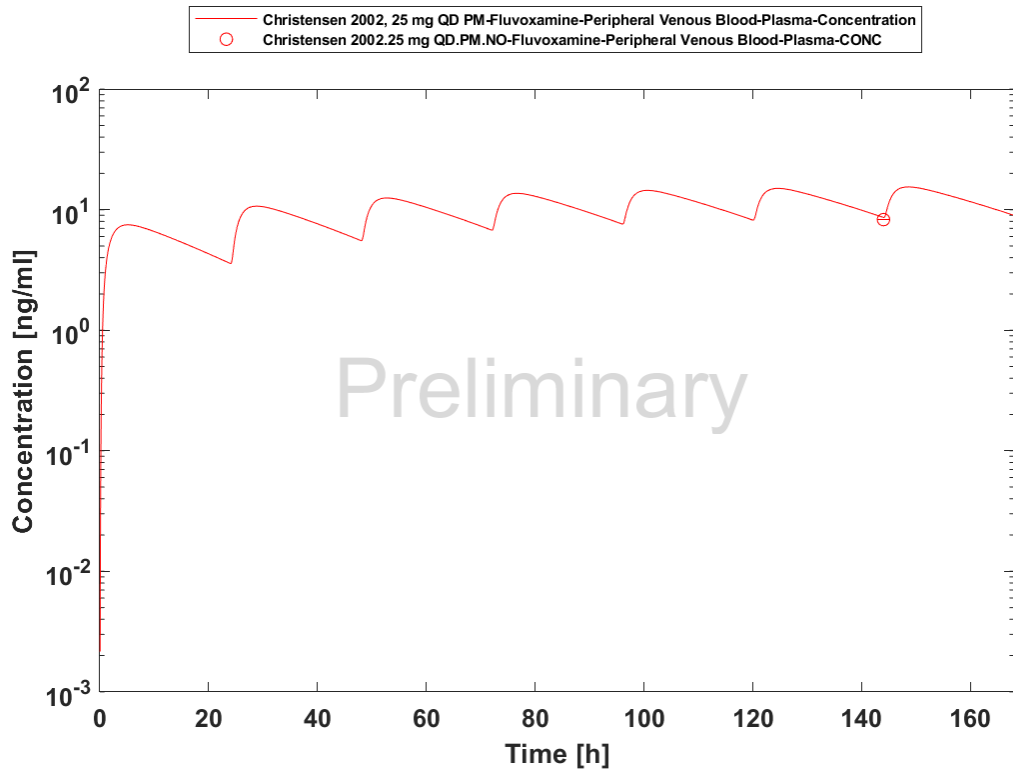
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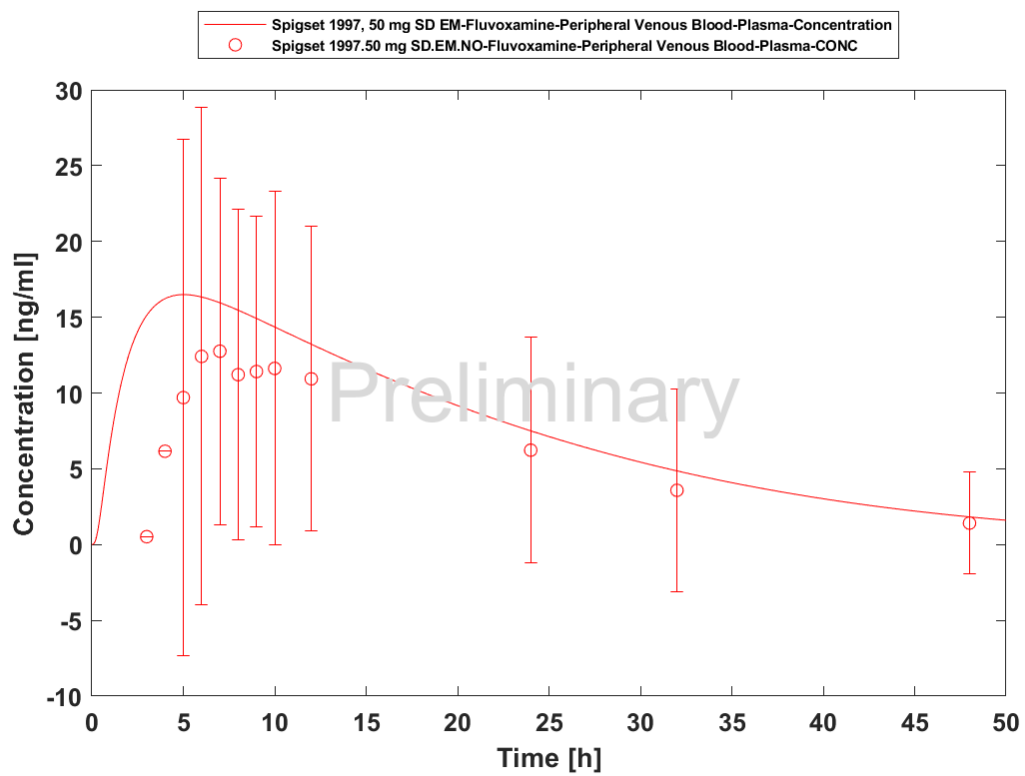
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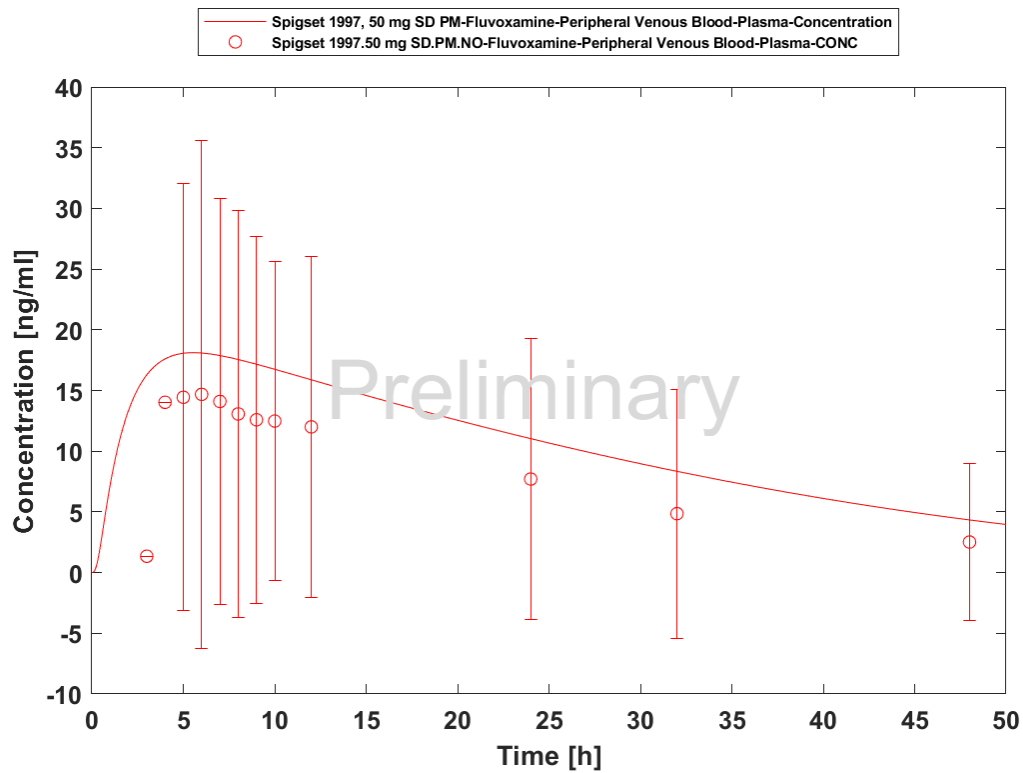
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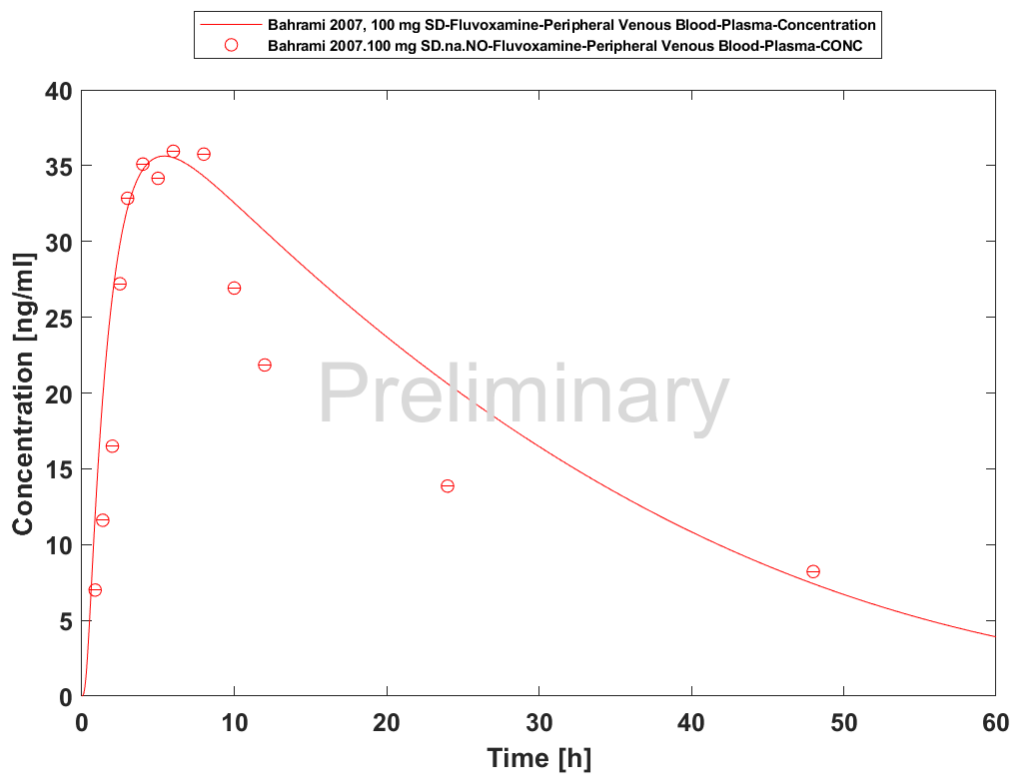
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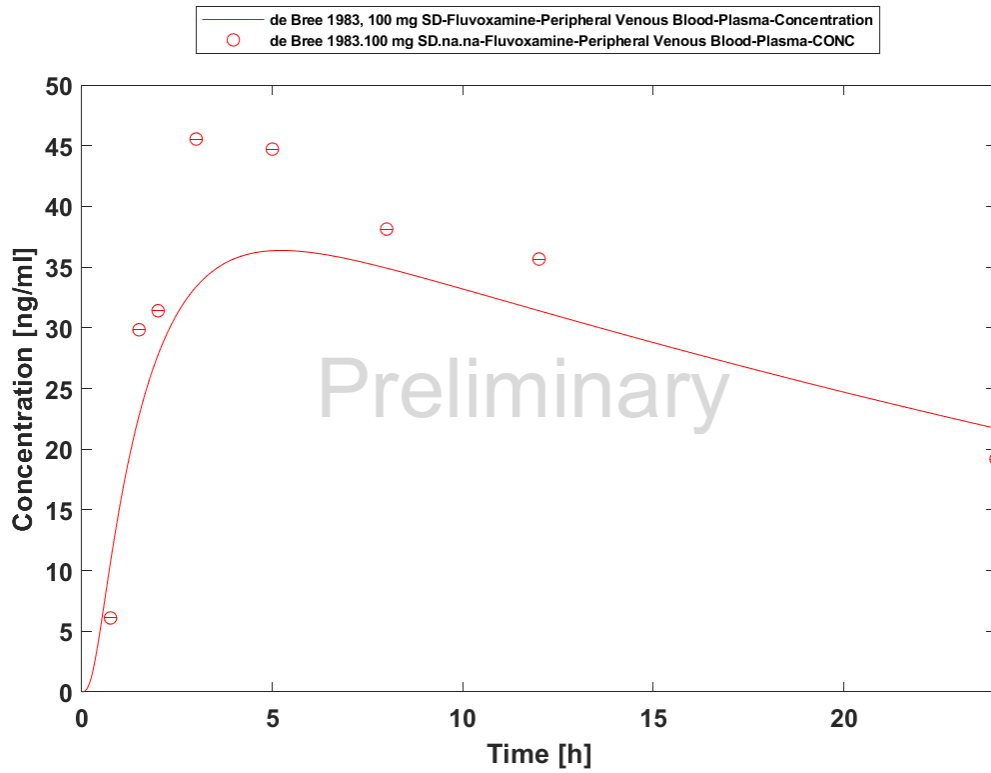
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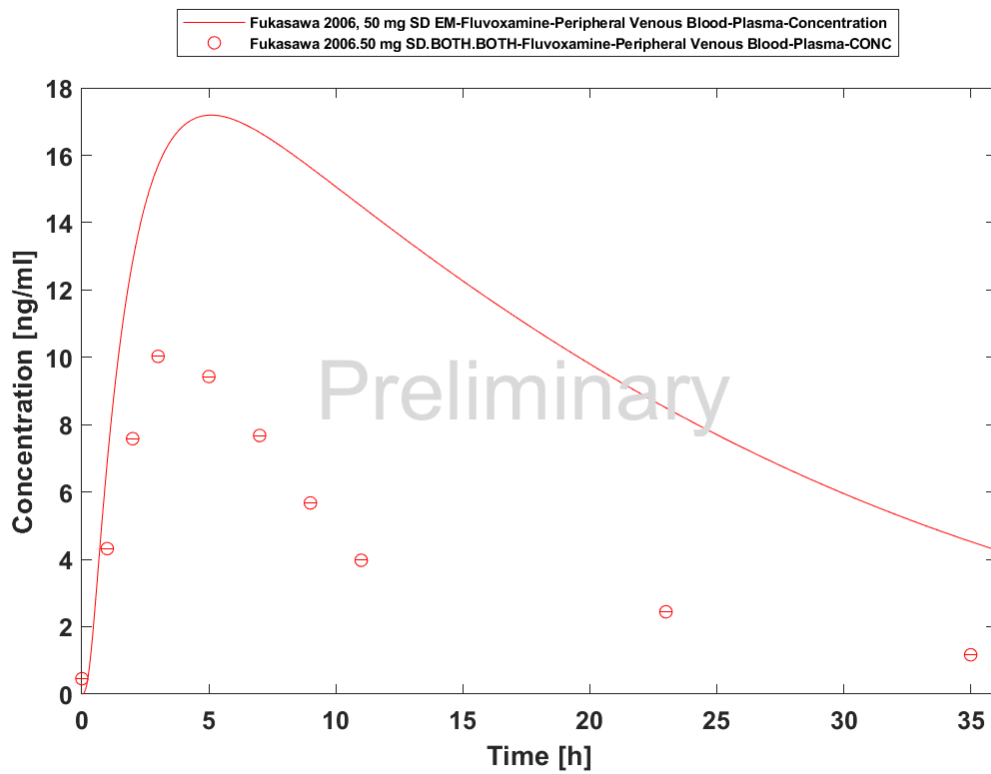
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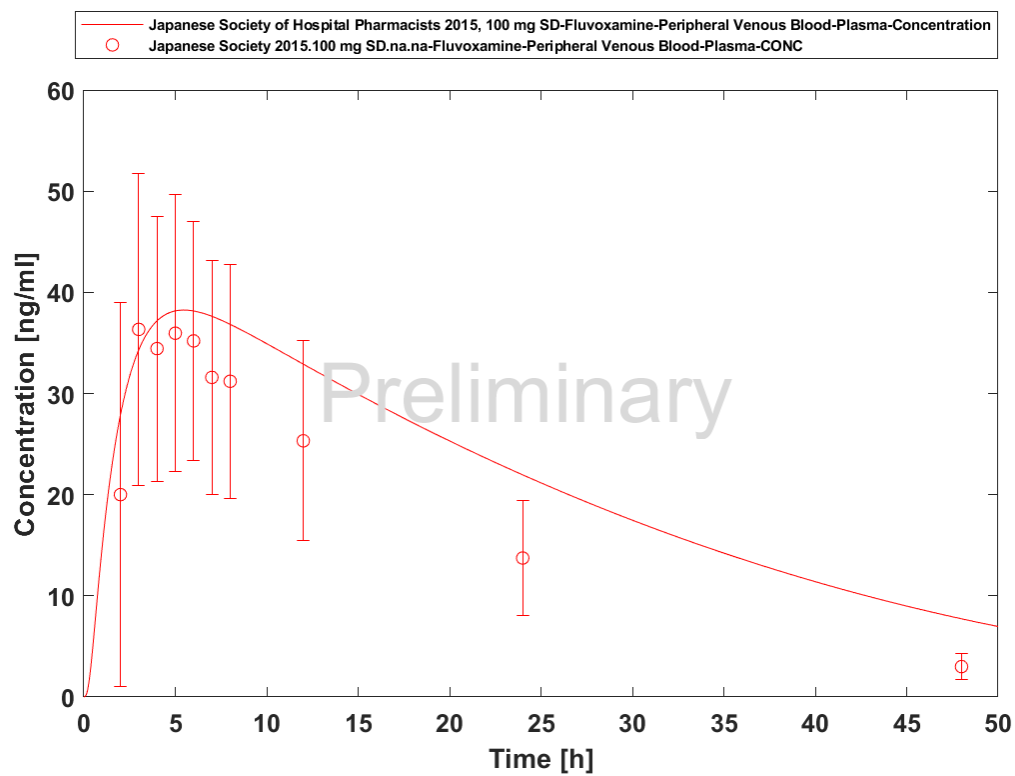
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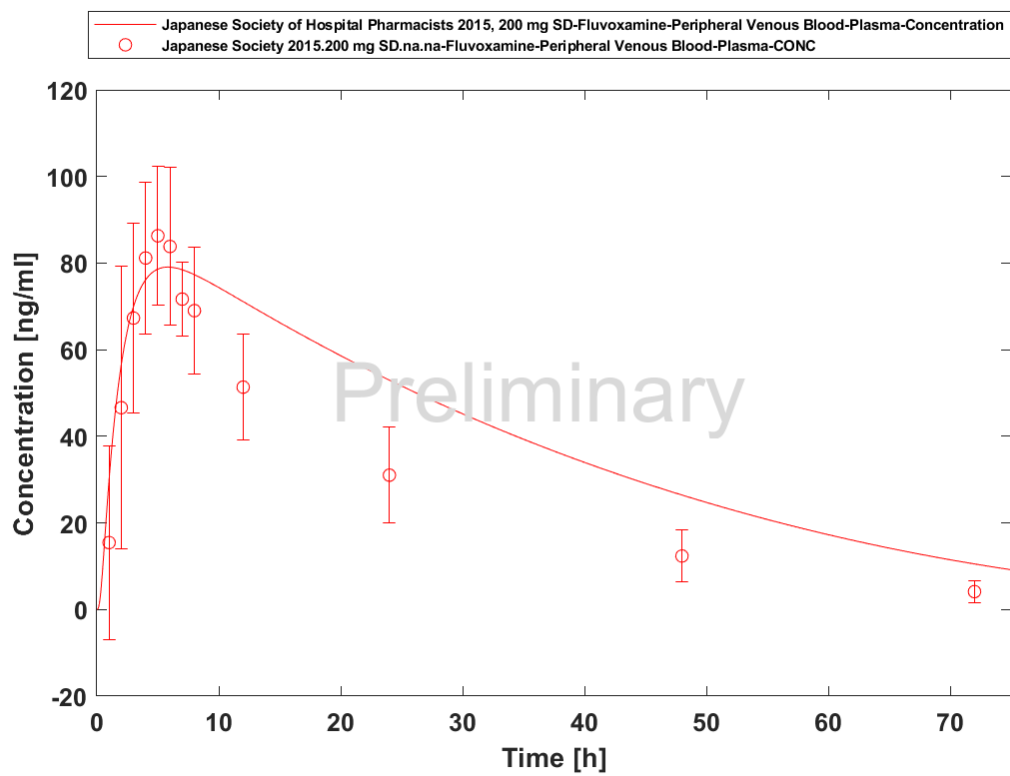
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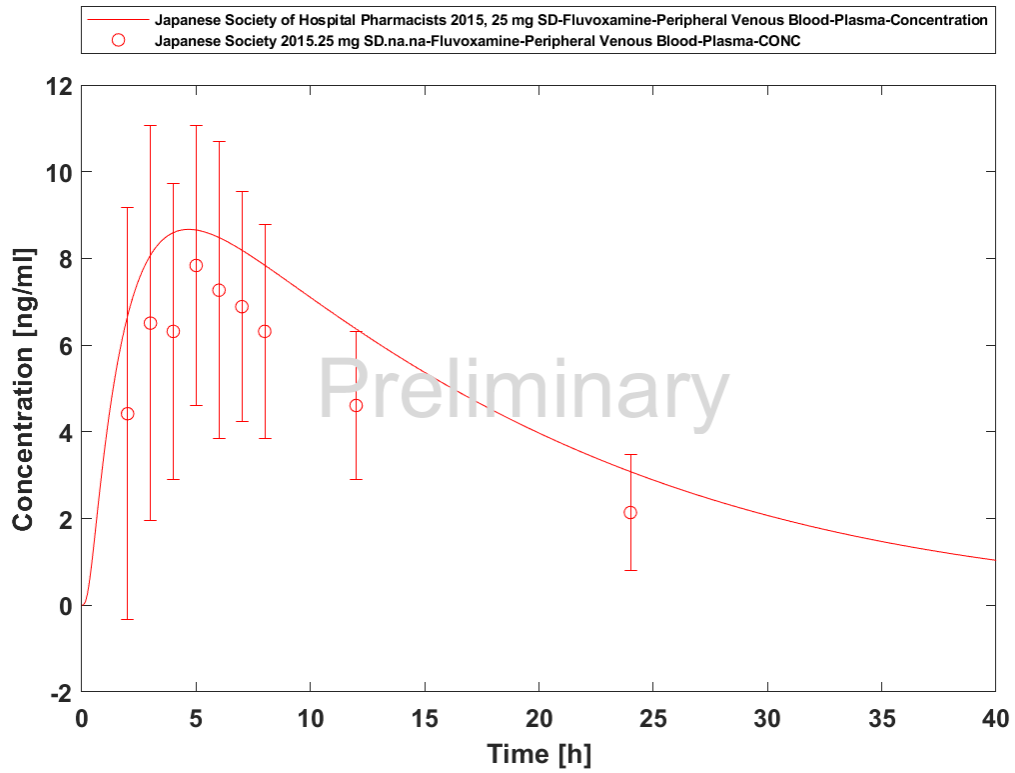
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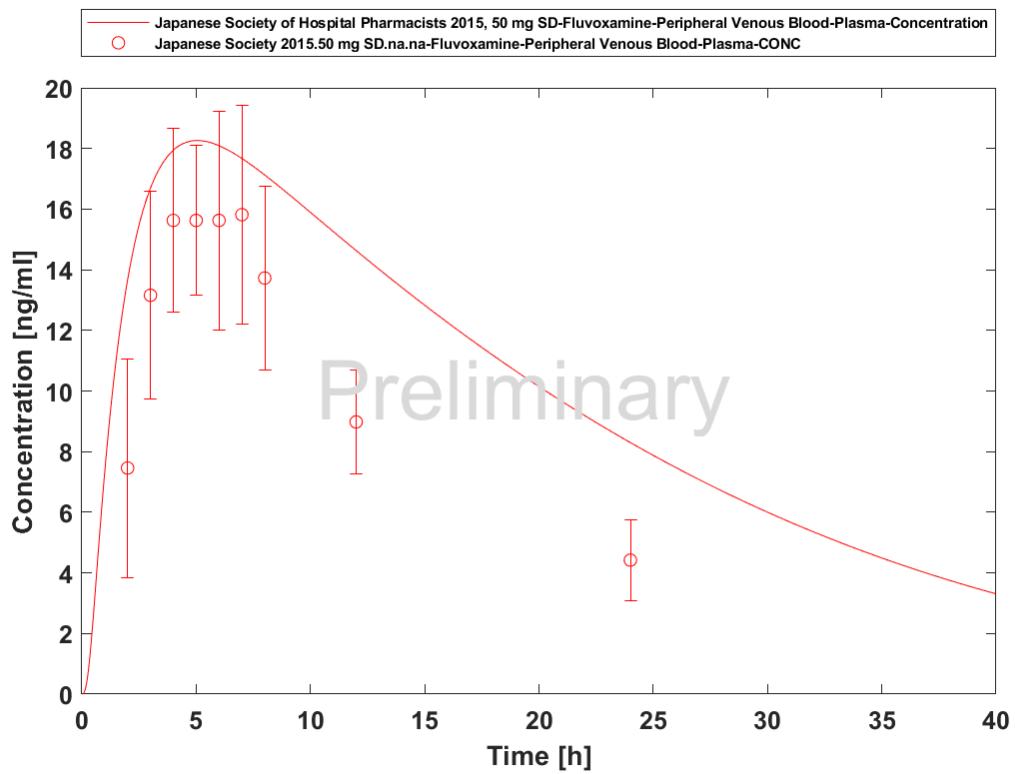
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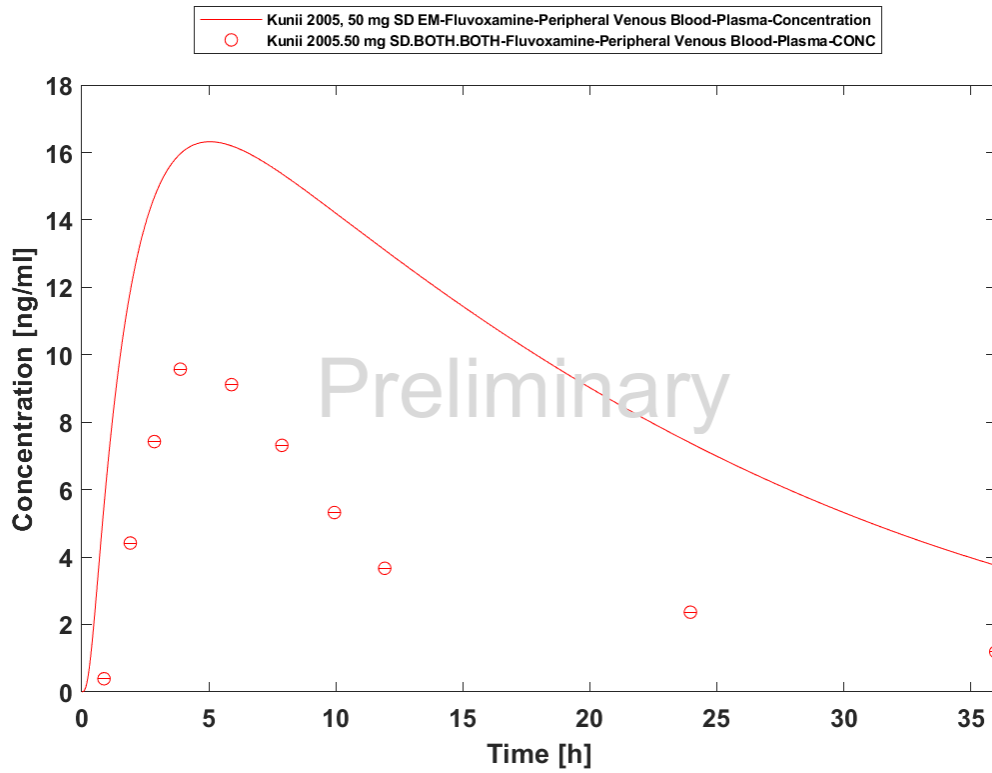
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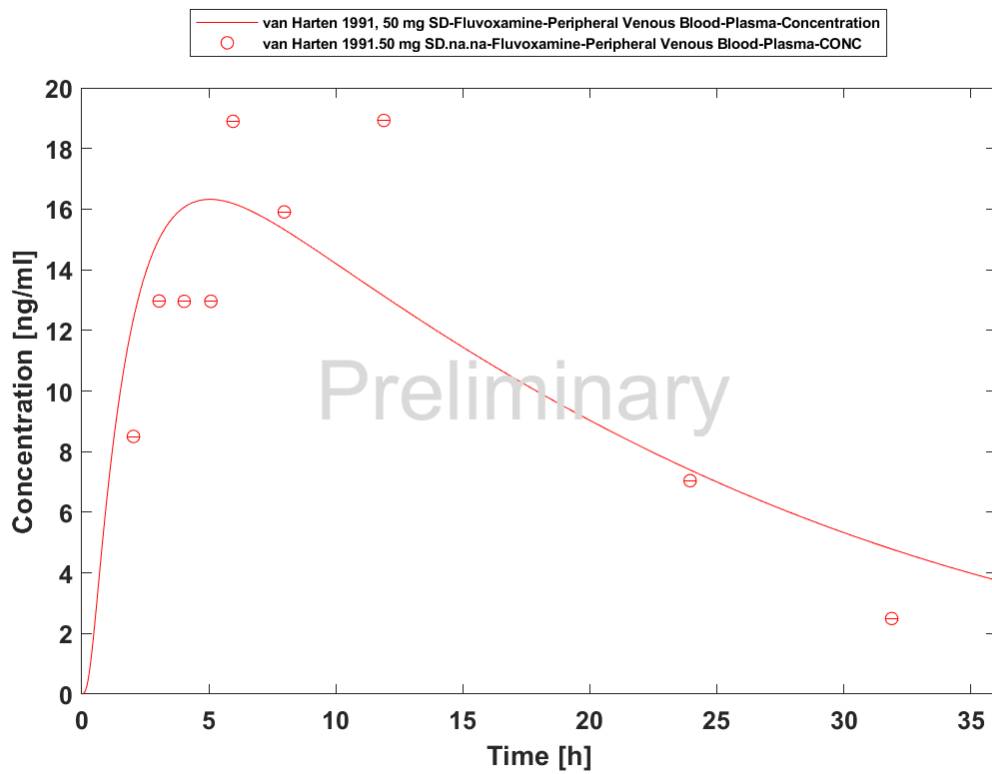
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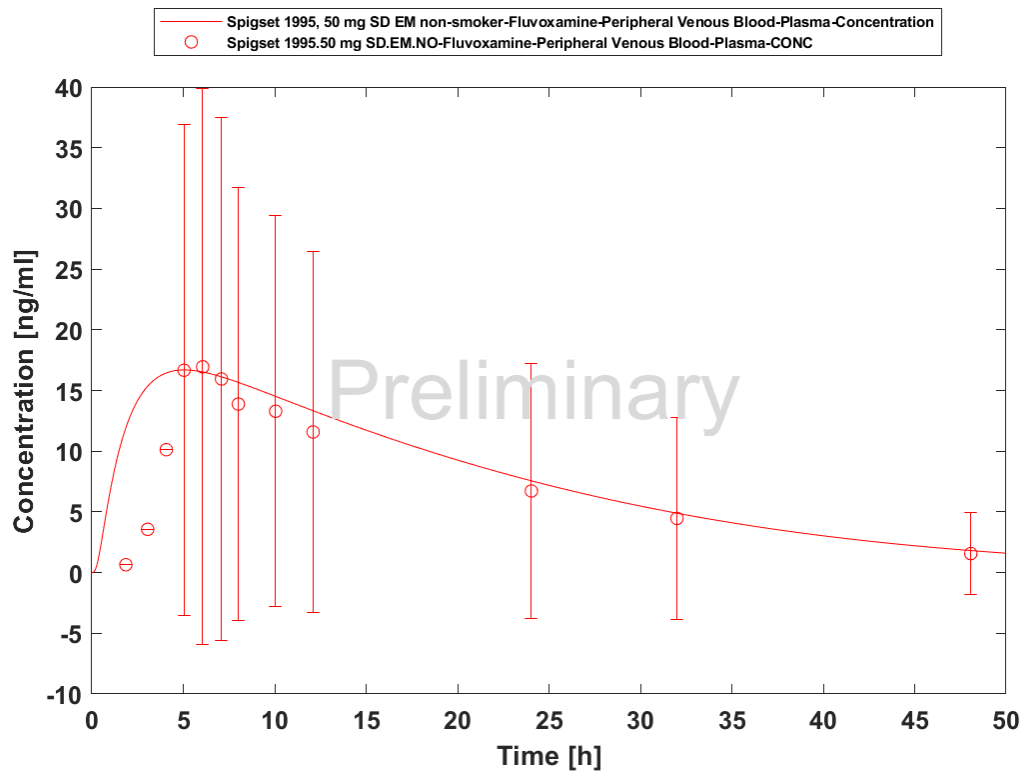
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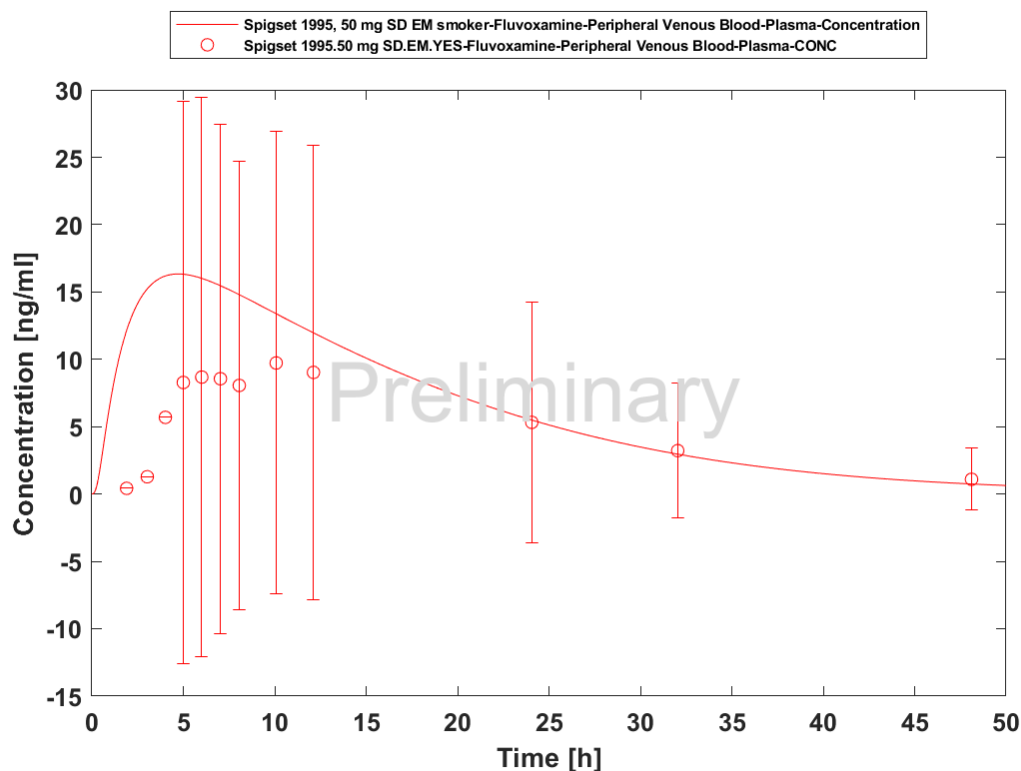
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4 Conclusion

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

In particular, it applies quantitative metabolism by CYP1A2 and CYP2D6. The inhibition of CYP1A2 and CYP3A4 are implemented and evaluated (shown elsewhere) in the current model as well. Thus, the model is fit for purpose to be applied for the prediction of drug-drug interaction

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MSDS material safety data sheet of fluvoxamine

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