

Building and evaluation of a PBPK model for Metformin in healthy adults

Version	1.0-OSP12.1
based on <i>Model Snapshot</i> and <i>Evaluation Plan</i>	https://github.com/Open-Systems-Pharmacology/Metformin-Model/releases/tag/v1.0
OSP Version	12.1
Qualification Framework Version	3.4

This evaluation report and the corresponding PK-Sim project file are filed at:

<https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/>

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1 Introduction

The presented model building and evaluation report evaluates the performance of a PBPK model for metformin in healthy adults.

The herein presented model was developed and published by Hanke et al. ([Hanke 2020](#)) and adjusted later on to PK-Sim V11 by re-optimizing OCT2.

Metformin is widely used as first-line treatment of type 2 diabetes. It is a highly hydrophilic compound, positively charged at physiological pH and depends on active transport for its absorption, distribution and excretion. The absorption of metformin is saturable and reported to be restricted to the upper intestine ([Vidon 1988](#)). The excretion of metformin is mainly mediated via the sequential action of OCT2 and MATE in the kidney, with a moderate contribution of renal glomerular filtration (approximately 20 %). Metformin is recommended by the FDA as OCT2/MATE victim drug for the use in clinical DDI studies and drug labeling ([FDA 2017](#)).

The herein presented PBPK model of metformin PBPK model has been developed and evaluated by comparing simulations to observed data of both intravenously and orally administered metformin covering a dosing range from 0.001 to 2550 mg.

The presented model includes the following features:

- transport by PMAT,
- transport by OCT1,
- transport by OCT2,
- transport by MATE,
- renal clearance by glomerular filtration,
- oral absorption with dissolution rate assigned to a Weibull function.

2 Methods

2.1 Modeling strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. ([Kuepfer 2016](#)). Relevant information on 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 ([Willmann 2007](#)). The information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

Transporters and metabolizing enzymes relevant to the pharmacokinetics of the modeled drugs were implemented in agreement with current literature, utilizing the PK-Sim® expression database ([PK-Sim Ontogeny Database Version 7.3](#)) or otherwise referenced for the specific process.

A model was built based on clinical data from studies with intravenous and oral administration of metformin. The studies reported individual or mean plasma concentrations of metformin, and some of the studies reported fraction excreted to urine. For the studies reporting intravenous administration, metformin was administered in doses of 0.001 to 1000 mg. For the studies reporting oral administration, metformin was administered in doses of 0.001–2550 mg.

Virtual mean individuals were generated for each study according to the published demographic information, with corresponding age, weight, height, sex, ethnicity, hematocrit and GFR, if available. If no information was provided, a default virtual individual was applied (30 years of age, male, European, mean weight, height, hematocrit and GFR characteristics from the PK-Sim® population database).

The clinical datasets for metformin PBPK modeling were divided into a model building dataset for model building and a test dataset for model evaluation and verification. Both datasets are presented in [Section 2.2](#).

A specific set of parameters ([Section 2.3.4.](#)) were optimized to describe the disposition of metformin using the Parameter Identification module provided in PK-Sim®. To limit the parameters to be optimized during model building, the minimal number of processes necessary to mechanistically describe the pharmacokinetics and drug-drug interactions (DDIs) of the modeled drugs were implemented into the models. The saturable absorption is implemented via PMAT and OCT1 in the small intestine. As late absorption of orally administered metformin is neither consistent with the reported plasma concentration time-profiles nor with the incomplete absorption of metformin, the relative expression of PMAT and OCT1 in the large intestinal mucosa was set to zero. Furthermore, no information regarding active transport processes at the basolateral side of the intestinal mucosa could be obtained. Therefore, the passive permeability from the intracellular to the interstitial space of the small intestinal mucosa was optimized.

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 used

2.2.1 In vitro and physicochemical data

A literature search was performed to collect available information on physicochemical properties of metformin. The obtained information from literature is summarized in the table below, and was used for model building. Final model parameters are stated in [Section 3.1](#).

Parameter	Unit	Value	Source	Description
MW	g/mol	129.16	Wishart 2006	Molecular weight
pK _a (base)		2.80	Desai 2014	Base dissociation constant
pK _b (base)		11.50	Desai 2014	Base dissociation constant
Solubility (pH 6.8)	g/L	350.90	Desai 2014	Solubility
logP		-1.43	Graham 2011	Partition coefficient between octanol and water
f _u	%	100	Tucker 1981, Pentikäinen 1979, Sirtori 1978	Fraction unbound
PMAT Hill		3	Zhou 2007	PMAT Hill coefficient, Literature value = 2.64
K _m OCT1	µmol/L	1180.00	Chen 2009	OCT1 Michaelis-Menten constant
K _m OCT2	µmol/L	810.00	Chen 2009	OCT2 Michaelis-Menten constant
K _m MATE1	µmol/L	283.00	Yin 2016	MATE1 Michaelis-Menten constant
Tablet fasted Weibull shape	-	1.36	Block 2008	Dissolution profile shape
Tablet fasted Weibull time	min	7.90	Block 2008	Dissolution time (50% dissolved)

2.2.2 Clinical data

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

The following publications were used for model building (training dataset) and model verification (test dataset):

Dose [mg]	Dosing	PK data	Dataset	Reference
0.00145	iv, bolus, sd	plasma, blood and tissue (kidney,liver, intestines and muscle)	training	Gormsen 2016
250	iv (15 min), sd	plasma, excretion into urine	training	Tucker 1981
500	iv (5 min), sd	plasma, excretion into urine	test	Pentikäinen 1979
1000	iv (bolus), sd	plasma, excretion into urine	training	Sirtori 1978
0.0008556	po, -, fasted, sd	plasma and tissue (kidney, liver, and muscle)	training	Gormsen 2016
10	po, sol, fasted, sd	plasma, excretion into urine	training	Stopfer 2018
250	po, tab, fed, qd	plasma, excretion into urine	test	Somogyi 1987
500	po, -, fasted, sd	plasma, excretion into urine	test	Wang 2008
500	po, sol, fasted, sd	plasma, excretion into urine, and tissue (kidney)	training	Boehringer 2018
500	po, tablet, fed, sd	plasma	test	Caillé 1993
500	po, tablet, fed, sd	plasma, excretion into urine	test	Gusler 2001
500	po, tablet, fasted, sd	plasma	test	Najib 2002
500	po, tablet, fasted, sd	plasma, excretion into urine	test	Pentikäinen 1979
500	po, tablet, fasted, sd	plasma, excretion into urine	test	Sambol 1996b
500	po, tablet, fasted, sd	plasma, excretion into urine	training	Stopfer 2016
500	po, tablet, fed, sd	plasma, excretion into urine	test	Tucker 1981
500	po, tablet, fed, bid	plasma, excretion into urine	test	DiCicco 2014
500 ^(a)	po, tablet, fasted, bid	plasma	test	Jang 2016
500 ^(a)	po, tablet, fasted, bid	plasma	test	Kim 2014
500	po, tablet, fasted, bid	plasma	test	Manitpisitkul 2014
500 ^(a)	po, tablet, fasted, bid	plasma	test	Oh 2016
750 ^(b)	po, tablet, fasted, bid	plasma	test	Cho 2011
750 ^(b)	po, tablet, fasted, bid	plasma	test	Cho 2014
750 ^(b)	po, tablet, fasted, bid	plasma	test	Ding 2014
850	po, sol, fasted, sd	plasma, excretion into urine	training	Sambol 1996b

Dose [mg]	Dosing	PK data	Dataset	Reference
850 (c)	po, tablet, fasted, bid	plasma	test	Chen 2009
850	po, tablet, fasted, sd	plasma	test	Morrissey 2016
850	po, tablet, fed, sd	blood, plasma	test	Robert 2003
850	po, tablet, fasted, sd	blood, plasma, excretion into urine	test	Sambol 1995
850	po, tablet, fasted, sd	plasma, excretion into urine	test	Sambol 1996a
850	po, tablet, fed, sd	plasma, excretion into urine	training	Sambol 1996b
850	po, tablet, fed, sd	plasma, excretion into urine	training	Sambol 1996b
850(c)	po, tablet, fasted, bid	plasma, excretion into urine	test	Hibma 2016
850	po, tablet, fasted, tid	plasma	test	Sambol 1996a
1000	po, tablet, fasted, sd	plasma, excretion into urine	test	Johansson 2014
1000	po, tablet, fasted, qd	plasma	test	Gan 2016
1500	po, tablet, fed, qd	plasma	test	Tucker 1981
1700	po, tablet, fasted, sd	plasma, excretion into urine	training	Sambol 1996a
2550	po, tablet, fasted, sd	plasma, excretion into urine	training	Sambol 1996a

(a) first dose 750 mg, second dose 500 mg

(b) first dose 1000 mg, second dose 750 mg

(c) first dose 1000 mg, second dose 850 mg

2.3 Model parameters and assumptions

2.3.1 Absorption

The parameter value for `Specific intestinal permeability` was optimized based on clinical oral data, see [Section 2.3.4](#). The saturable absorption is implemented via PMAT and OCT1 in the small intestine. As late absorption of orally administered metformin is neither consistent with the reported plasma concentration time-profiles nor with the incomplete absorption of metformin, the relative expression of PMAT and OCT1 in the large intestinal mucosa was set to zero. Additionally, no information regarding active transport processes at the basolateral side of the intestinal mucosa could be obtained, therefore, the passive basolateral permeability `(P (intracellular -> interstitial))` was optimized, see [Section 2.3.4](#).

The measured solubility of metformin hydrochloride in a phosphate buffer at pH 6.8 was used in the model (see [Section 2.2.1](#)).

The dissolution of tablets was implemented via empirical Weibull dissolution.

2.3.2 Distribution

Metformin is not bound to plasma proteins ($fu = 100\%$) (see [Section 2.2.1](#)) ([Sirtori 1978](#), [Pentikäinen 1979](#) and [Tucker 1981](#)). A value of 100% was used in this PBPK model for [Fraction unbound \(plasma, reference value\)](#). The major binding partner was set to albumin (see [Section 2.2.1](#)).

An important parameter influencing the resulting volume of distribution is lipophilicity. The reported experimental logP of -1.43 was used in this model (see [Section 2.2.1](#)).

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 [PK-SIM Standard](#) and cellular permeability calculation by [Charged dependent Schmitt normalized to PK-SIM](#).

2.3.3 Metabolism and Elimination

Following its absorption, metformin is not bound to plasma proteins, not metabolized, and not secreted to bile. Metformin is excreted unchanged with the urine by passive glomerular filtration and active renal secretion through the sequential action of organic cation transporter 2 (OCT2) and multidrug and toxin extrusion protein 1 (MATE1). The transport proteins involved in metformin PK were implemented in the model as described below:

- PMAT

The PMAT expression profiles are based on high-sensitive real-time RT-PCR ([Nishimura 2005](#)). Metabolic enzyme activity was described as saturable process following Hill kinetics, where the [PMAT Hill](#) was taken from literature and [K_m](#) and [k_{cat}](#) were optimized based on clinical data (see [Section 2.3.4](#)).

- OCT1

The OCT1 expression profiles are based on Microarray expression data ([Kolesnikov 2015](#)). Transporter activity was described as saturable process following Michaelis-Menten kinetics, where the [K_m](#) was taken from literature and [k_{cat}](#) was optimized based on clinical data (see [Section 2.3.4](#)).

- OCT2

The OCT2 expression profiles are based on Expressed Sequence Tags (EST) ([NCBI 2019](#)). Transporter activity was described as saturable process following Michaelis-Menten kinetics, where the [K_m](#) was taken from literature and [k_{cat}](#) was optimized based on clinical data (see [Section 2.3.4](#)).

- MATE1

The MATE1 expression profiles assumed 100% expression in the Kidney ([Otsuka 2005](#) and [Masuda 2006](#)). Transporter activity was described as saturable process following Michaelis-Menten kinetics, where the [K_m](#) was taken from literature and [k_{cat}](#) was optimized based on clinical data (see [Section 2.3.4](#)).

Additionally, passive renal clearance by glomerular filtration was implemented and the [GFR fraction](#) was set to 1. In addition, fraction of bile that was continuously released was set to 1 ([EHC continuous fraction](#))

2.3.4 Automated Parameter Identification

The following parameters have been estimated in the model:

Model Parameter

Km (PMAT)

kcat (PMAT)

kcat (OCT1)

kcat (OCT2)

kcat (MATE1)

Specific intestinal permeability

Basolateral small intestinal permeability

Basolateral large intestinal permeability

Tablet dissolution fed Weibull Shape

Tablet dissolution fed Weibull Time

3 Results and Discussion

The next sections show:

1. the final model input 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 Metformin final input parameters

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

Compound: Metformin

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	350.9 mg/ml		Measurement	True
Reference pH	6.8		Measurement	True
Lipophilicity	-1.43 Log Units		Measurement	True
Fraction unbound (plasma, reference value)	100 %		Measurement	True
Specific intestinal permeability (transcellular)	8.4891040357E-07 cm/min	Parameter Identification-Parameter Identification-Value updated from '17_final' on 2019-04-09 09:52	Fit	True
Is small molecule	Yes			
Molecular weight	129.1636 g/mol			
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	PK-Sim Standard
Cellular permeabilities	Charge dependent Schmitt normalized to PK-Sim

Processes

Systemic Process: Glomerular Filtration-GFR

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	1	

Transport Protein: OCT1-Paper

Molecule: OCT1

Parameters

Name	Value	Value Origin
Transporter concentration	1 µmol/l	
Vmax	641.185138023 µmol/l/min	Parameter Identification-Parameter Identification
Km	1180 µmol/l	

Transport Protein: OCT2-Paper

Molecule: OCT2

Parameters

Name	Value	Value Origin
Transporter concentration	1 µmol/l	
Vmax	17479.74 µmol/l/min	Parameter Identification-Parameter Identification
Km	810 µmol/l	

Transport Protein: MATE1-Paper

Molecule: MATE1

Parameters

Name	Value	Value Origin
Transporter concentration	1 µmol/l	
Vmax	165.69 µmol/l/min	Parameter Identification-Parameter Identification
Km	283 µmol/l	Parameter Identification-Parameter Identification

Transport Protein: PMAT-Paper

Parameters

Name	Value	Value Origin
Transporter concentration	1 $\mu\text{mol/l}$	
Vmax	76.4673688119 $\mu\text{mol/l/min}$	Parameter Identification-Parameter Identification-Value updated from '17_final' on 2019-04-09 09:51
Km	367.5702930377 $\mu\text{mol/l}$	Parameter Identification-Parameter Identification-Value updated from '17_final' on 2019-04-09 09:52
Hill coefficient	3	

3.2 Metformin 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.

Table 3-1: GMFE for Goodness of fit plot for concentration in plasma.

Group	GMFE
Metformin iv (model building)	1.24
Metformin iv (model verification)	1.23
Metformin oral administration (model building)	1.37
Metformin oral administration (model verification)	1.43
All	1.39

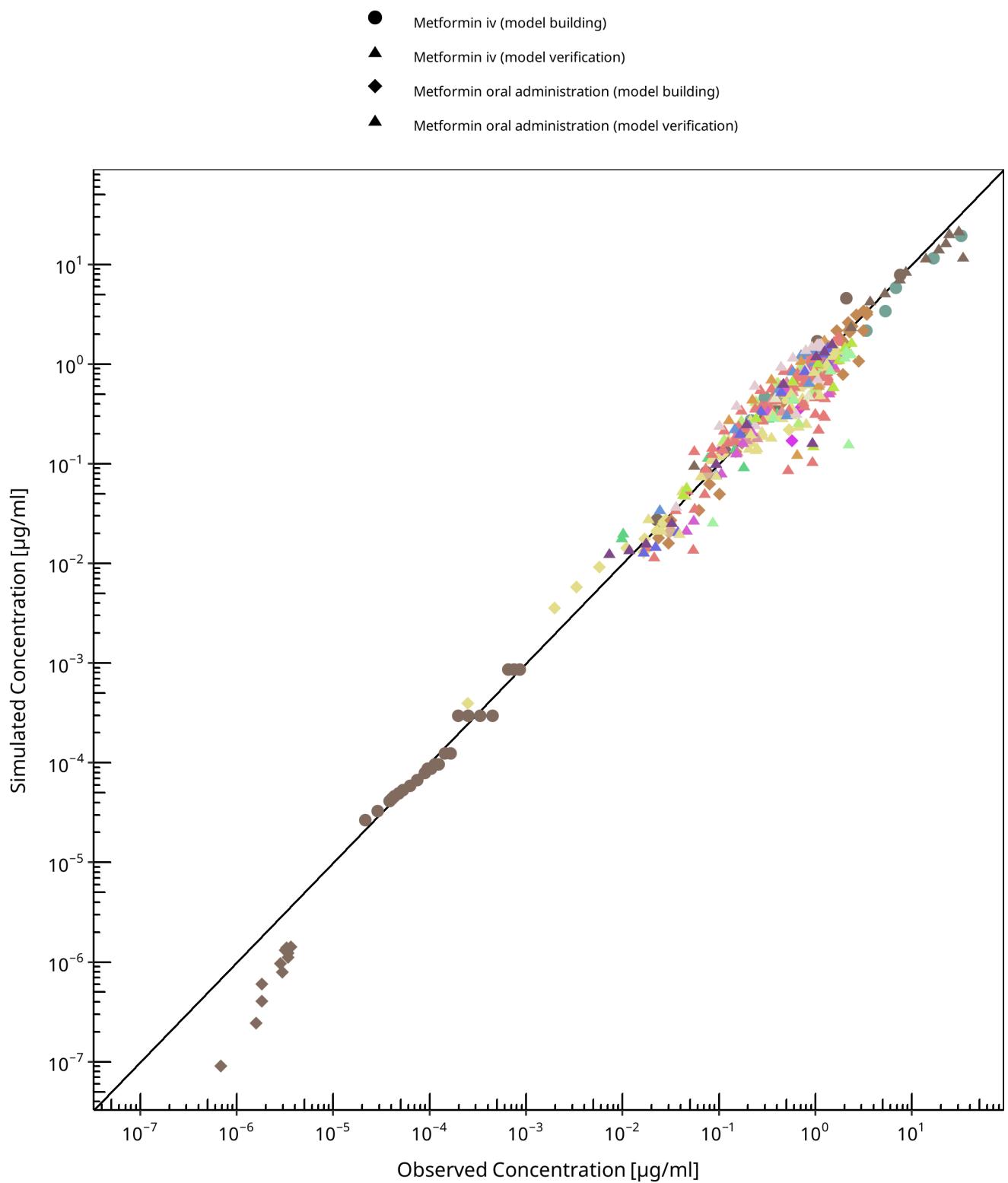


Figure 3-1: Goodness of fit plot for concentration in plasma.

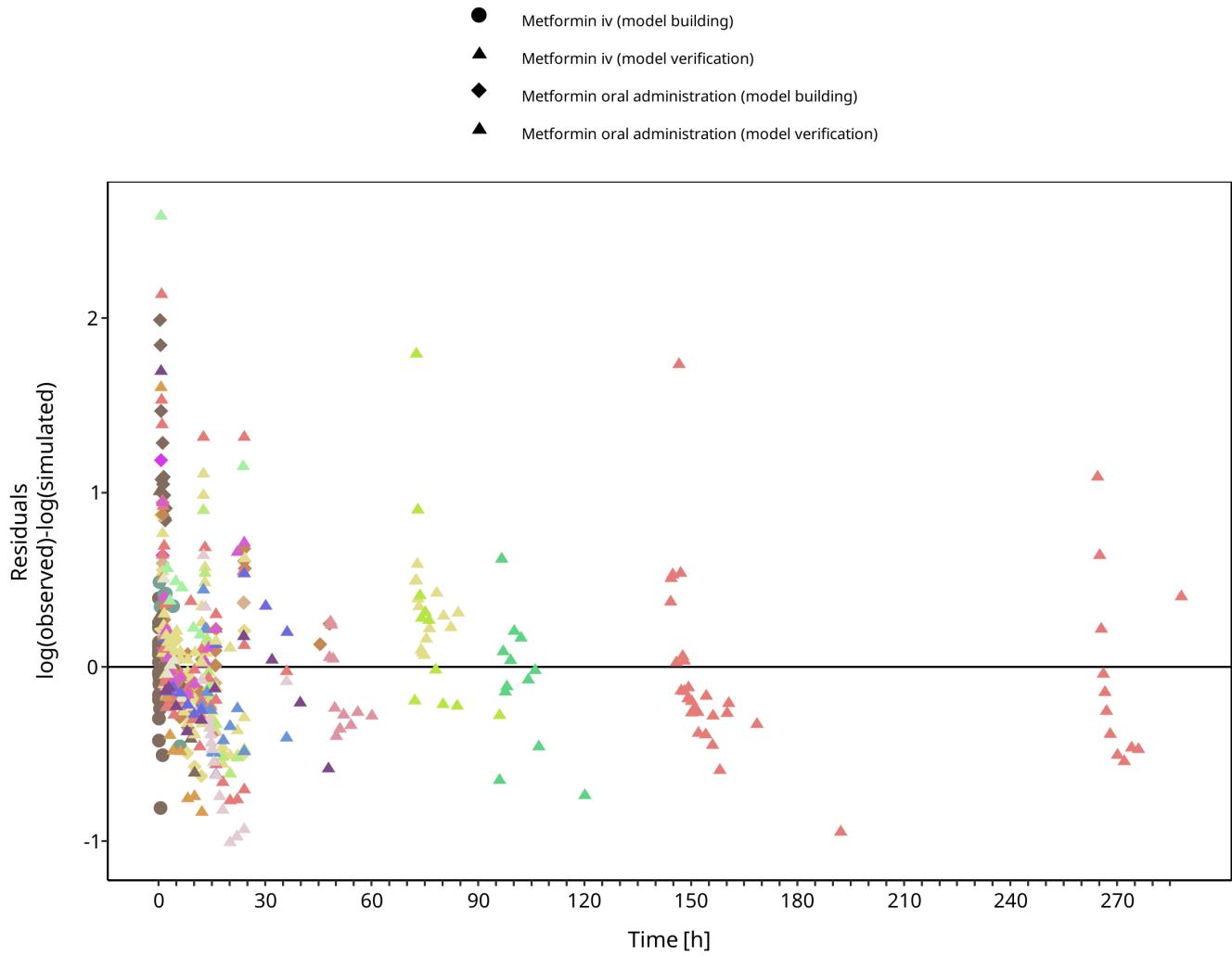


Figure 3-2: Goodness of fit plot for concentration in plasma.

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

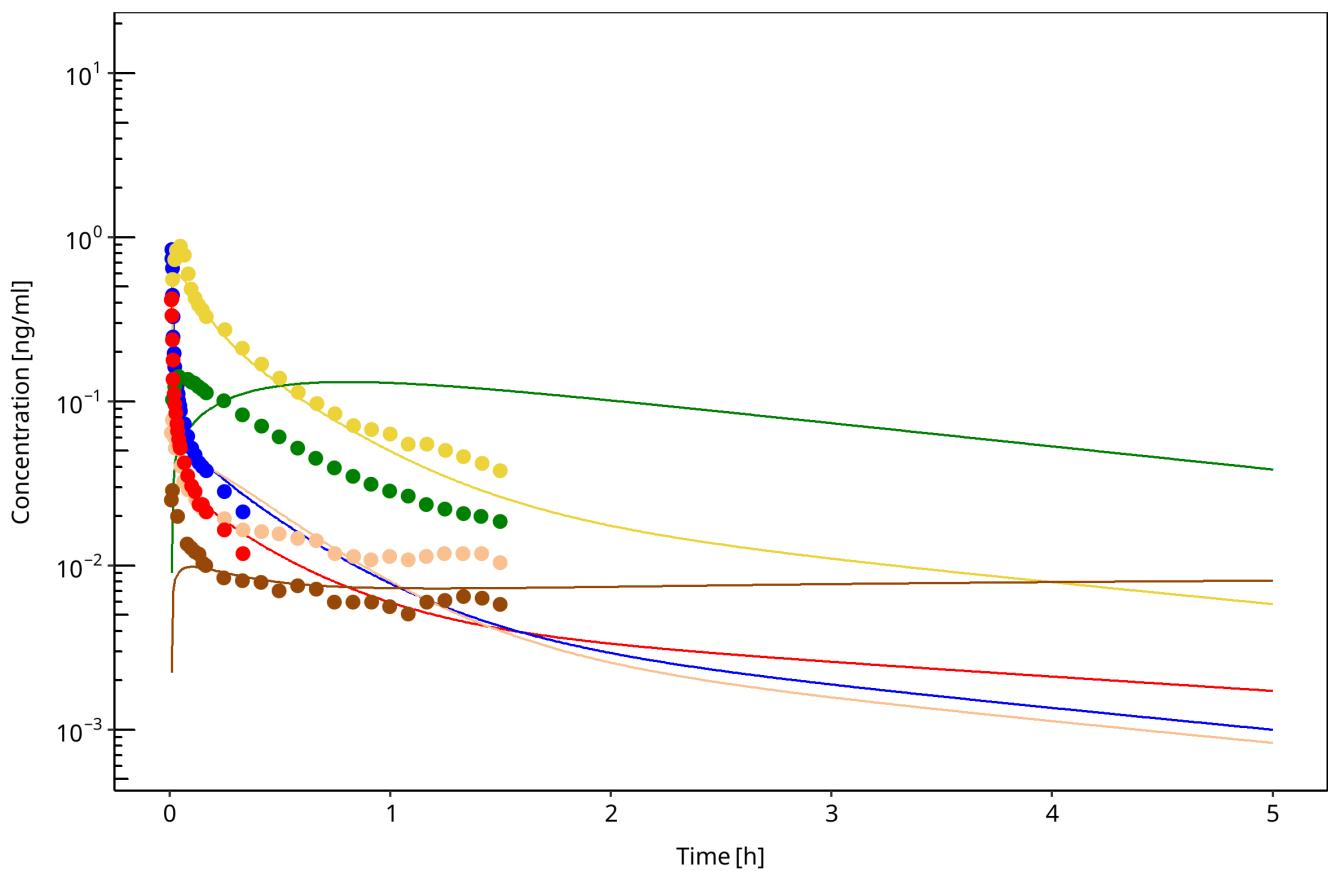
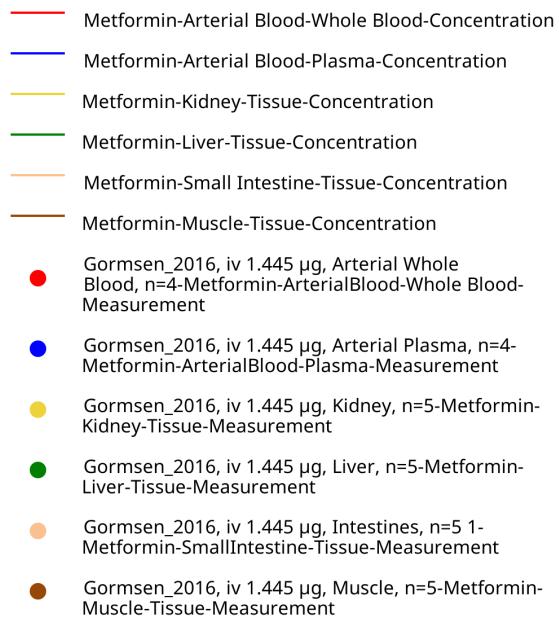


Figure 3-3: Metformin - iv, 0.0014 mg_Gormsen 2016

- iv 250 mg, Tucker 1981, n=4-Peripheral Venous Blood-Plasma-Concentration
— — iv 250 mg, Tucker 1981, n=4-Kidney-Urine-Fraction excreted to urine
● Tucker_1981, iv 195 mg, Plasma, n=4-Metformin-Peripheral Venous Blood-Plasma-Measurement
● Tucker_1981, iv 195 mg, Urine, n=4-Metformin-Kidney-Urine-Measurement
● Tucker_1981, iv, 195 mg, ID1-Metformin-Peripheral Venous Blood-Plasma-Measurement
● Tucker_1981, iv, 195 mg, ID2-Metformin-Peripheral Venous Blood-Plasma-Measurement
● Tucker_1981, iv, 195 mg, ID3-Metformin-Peripheral Venous Blood-Plasma-Measurement
● Tucker_1981, iv, 195 mg, ID4-Metformin-Peripheral Venous Blood-Plasma-Measurement
● Tucker_1981, iv, Urine, ID1-Metformin-Kidney-Urine-Measurement
● Tucker_1981, iv, Urine, ID2-Metformin-Kidney-Urine-Measurement
● Tucker_1981, iv, Urine, ID3-Metformin-Kidney-Urine-Measurement
● Tucker_1981, iv, Urine, ID4-Metformin-Kidney-Urine-Measurement

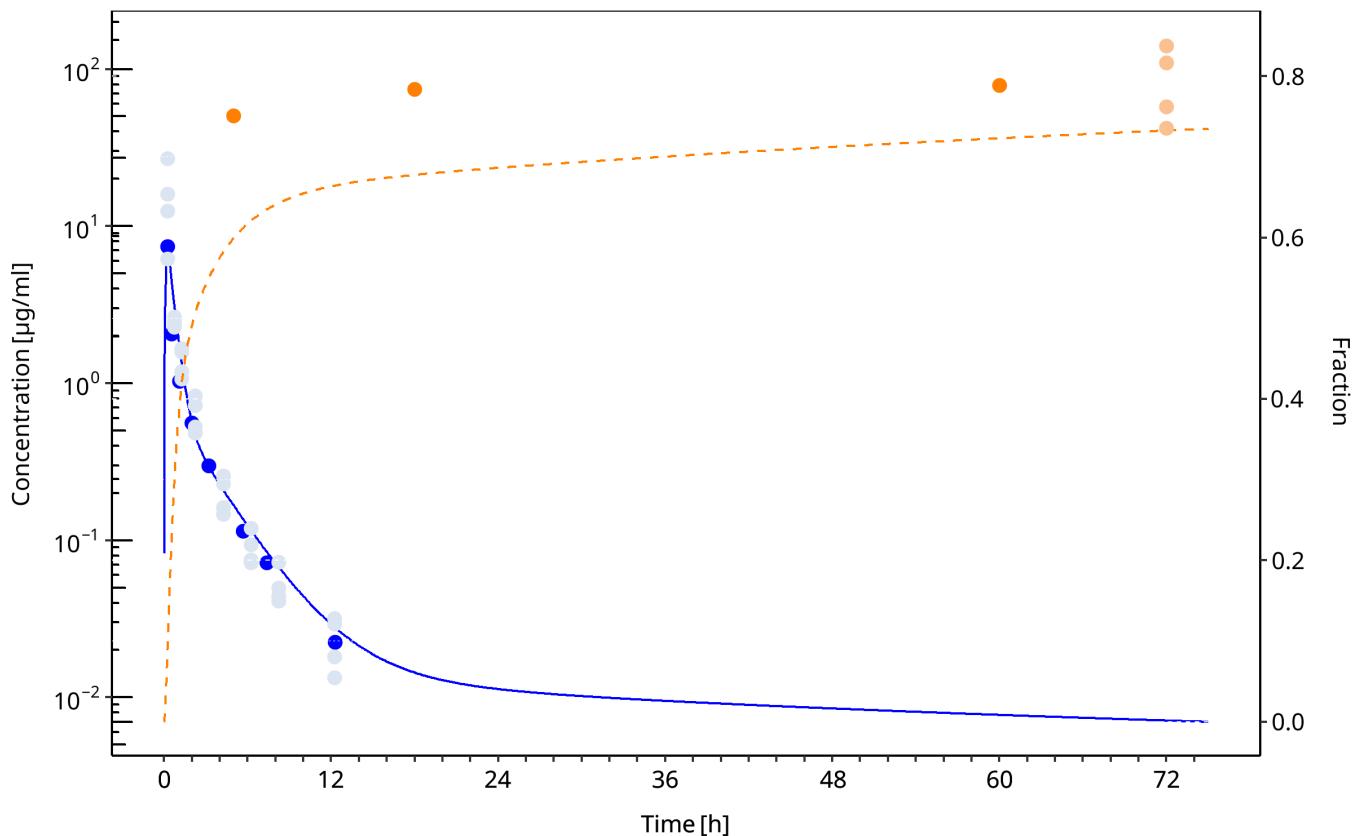


Figure 3-4: Metformin - iv, 250 mg_Tucker 1981

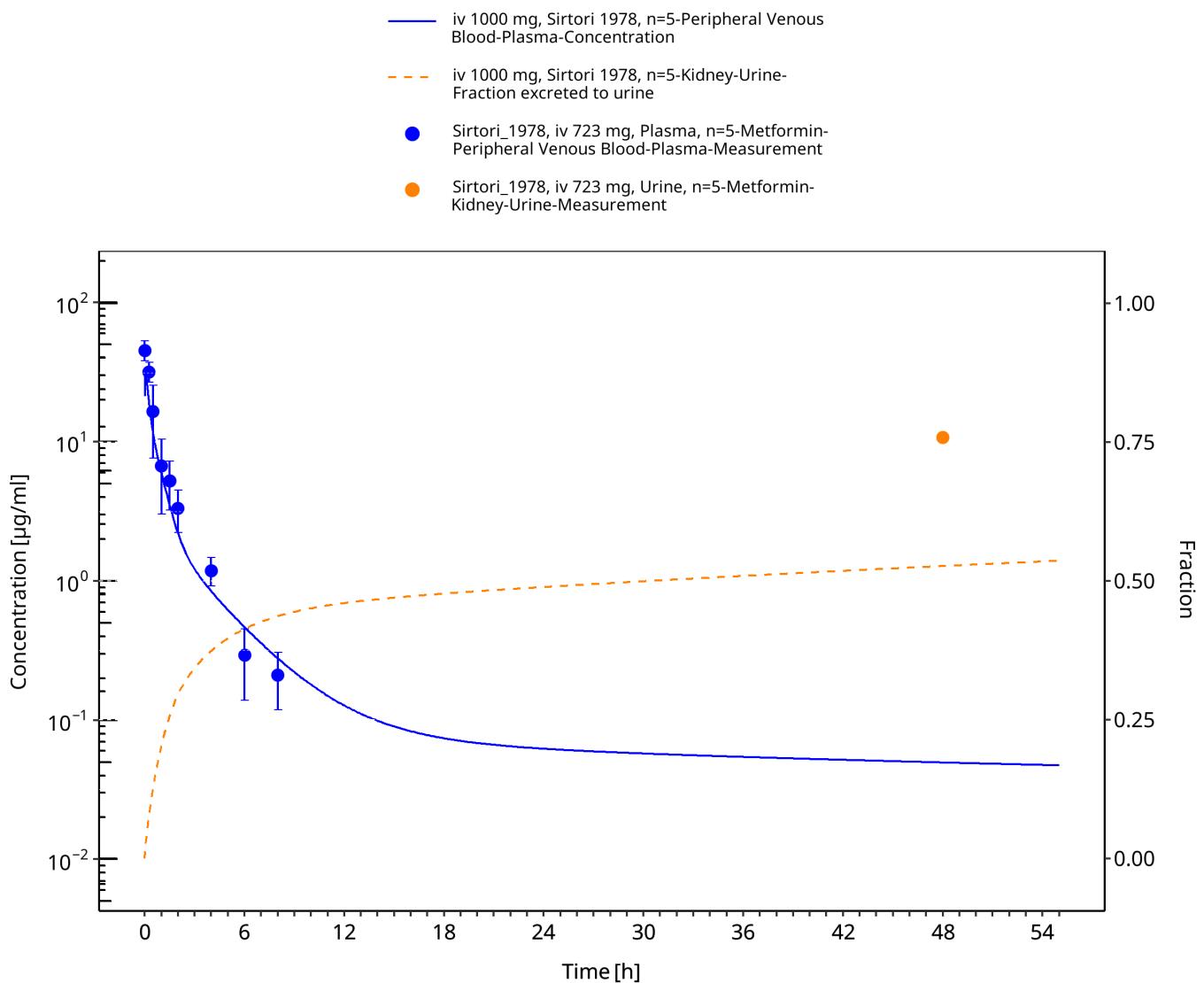


Figure 3-5: Metformin - iv, 1000 mg_Sirtori 1978

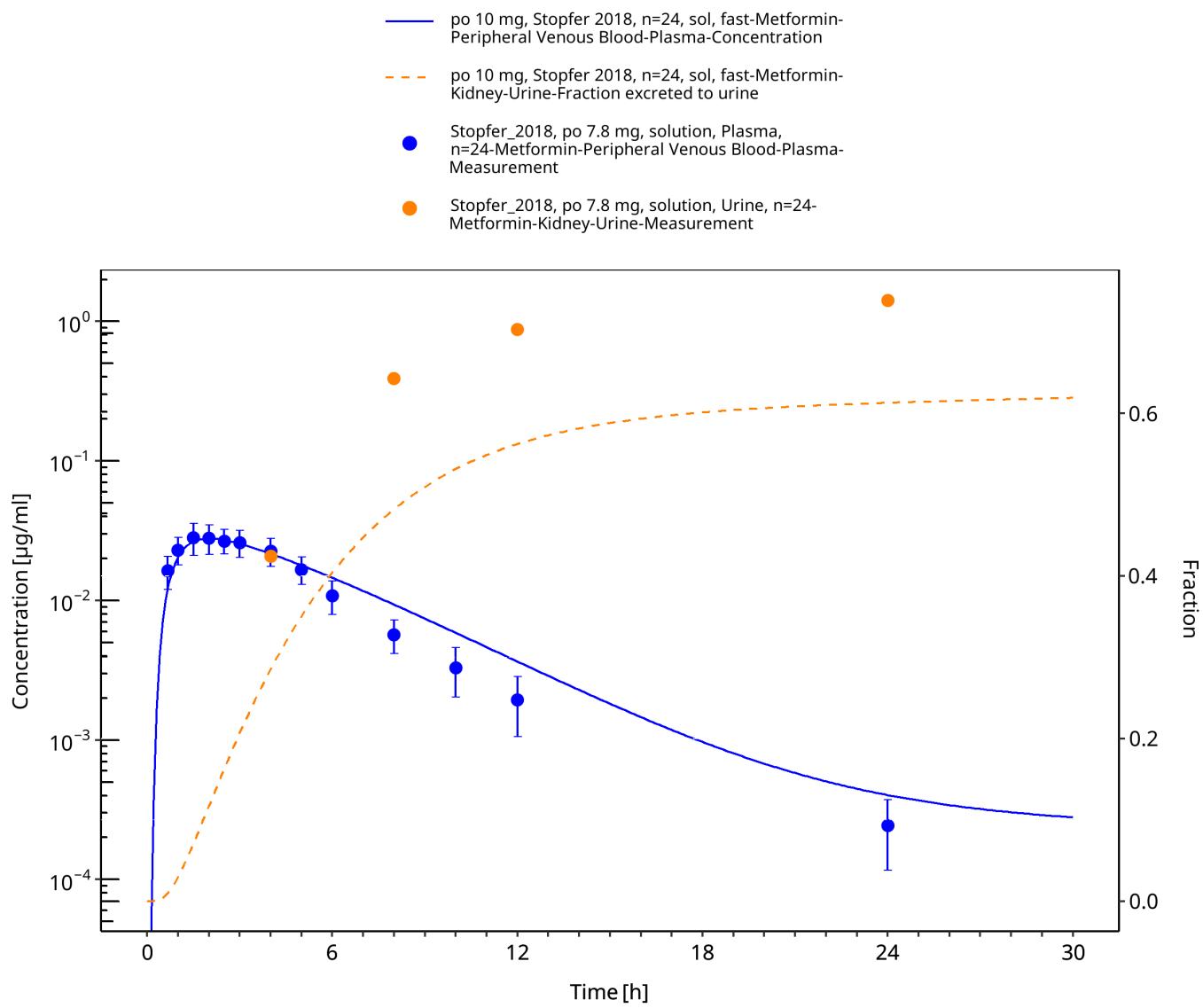


Figure 3-6: Metformin - po (sol) 10 mg_Stopfer 2018

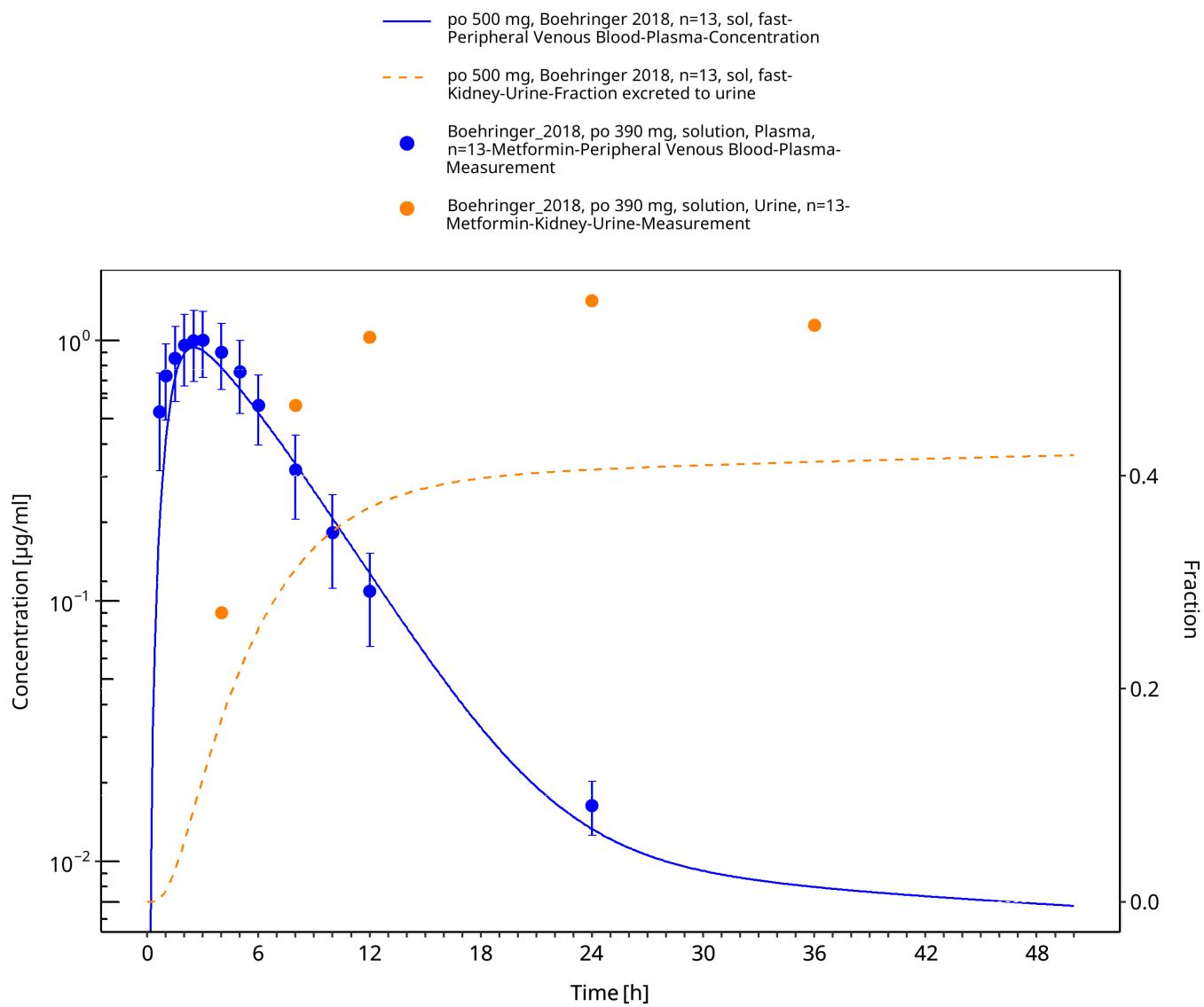


Figure 3-7: Metformin - po (sol) 500 mg_Behringer 2018

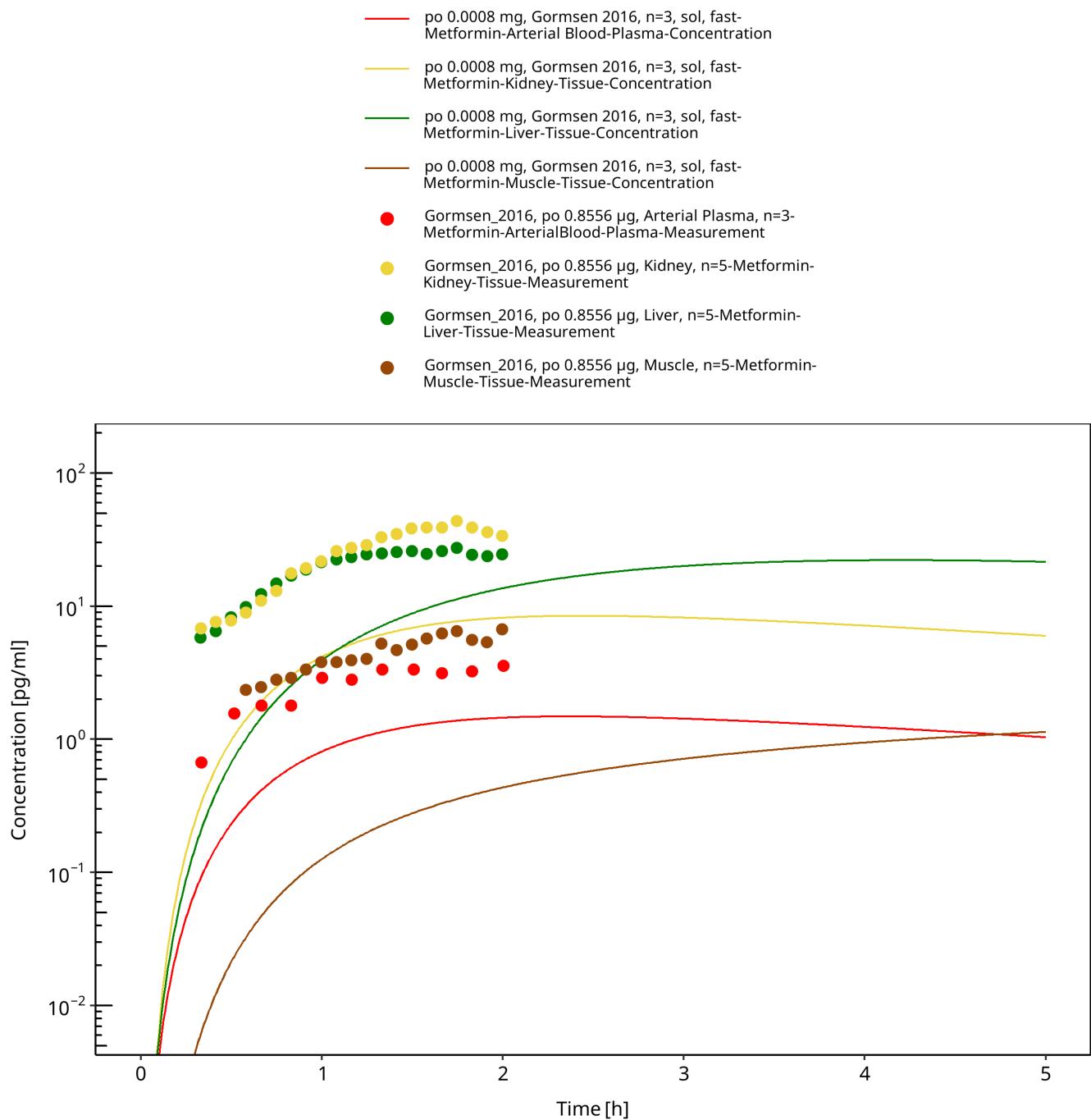


Figure 3-8: Metformin - po (sol) 0.0008 mg, Gormsen 2016

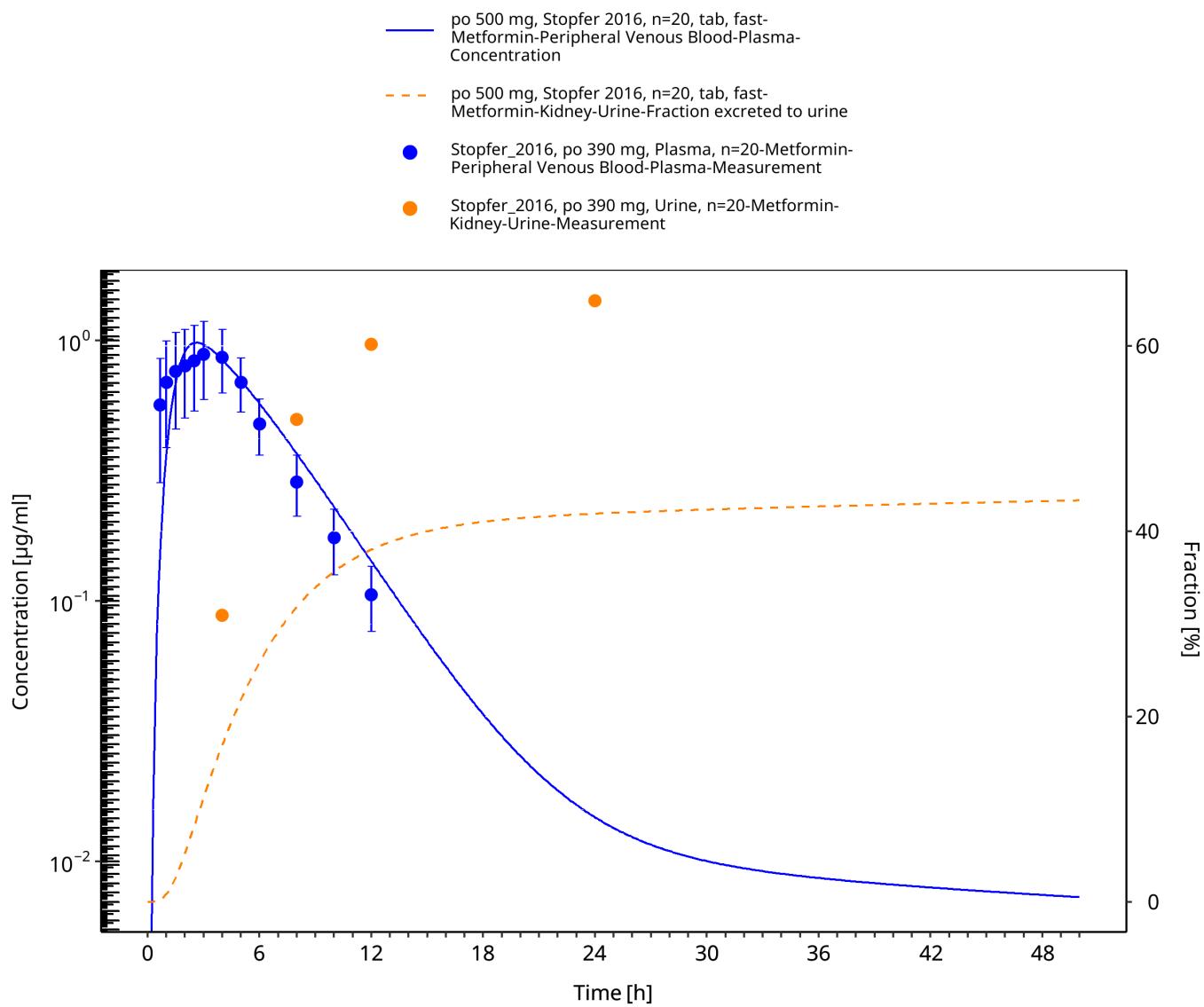


Figure 3-9: Metformin - po (tab) 500 mg_Stopfer 2016

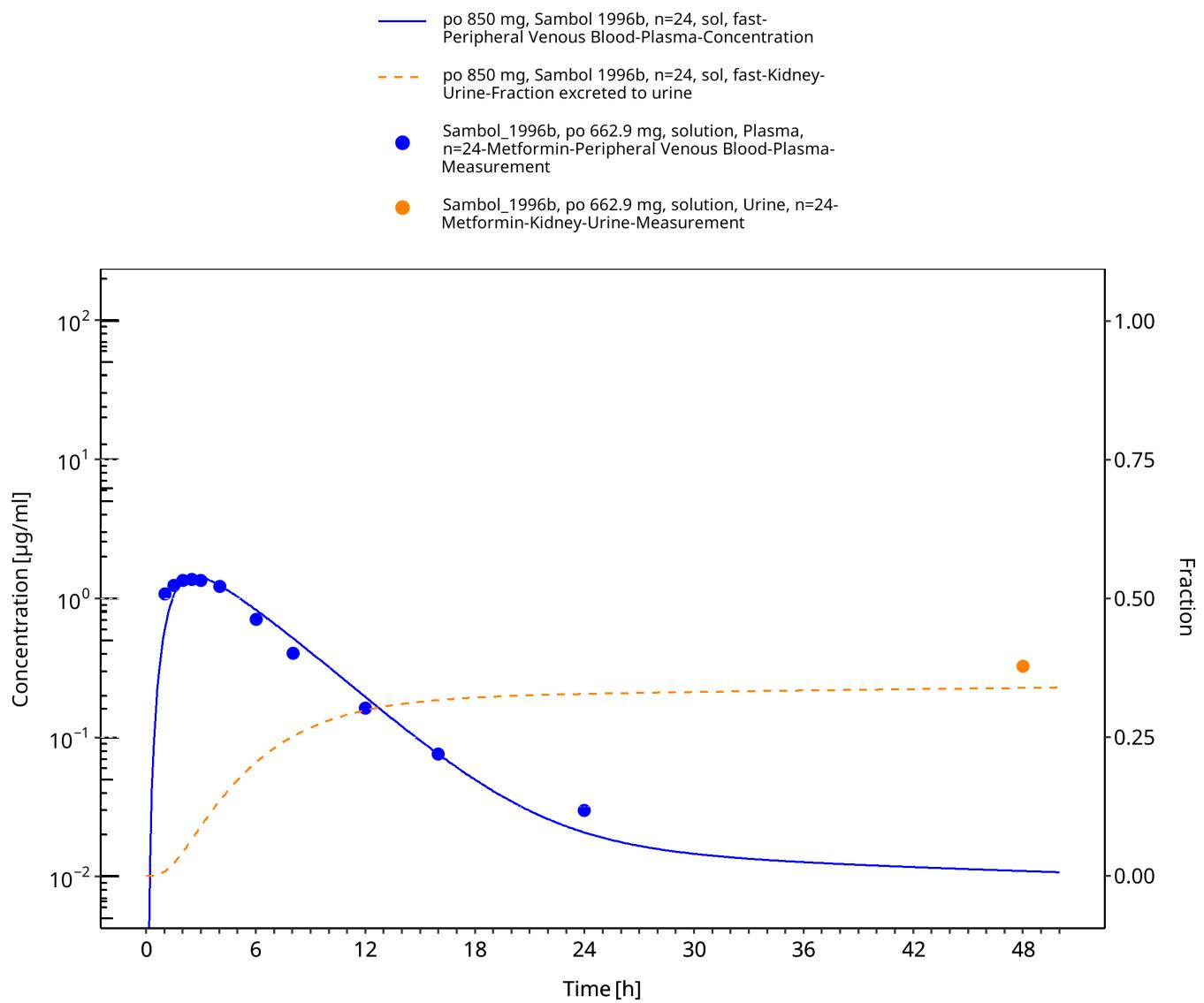


Figure 3-10: Metformin - po (sol) 850 mg_Sambol 1996b

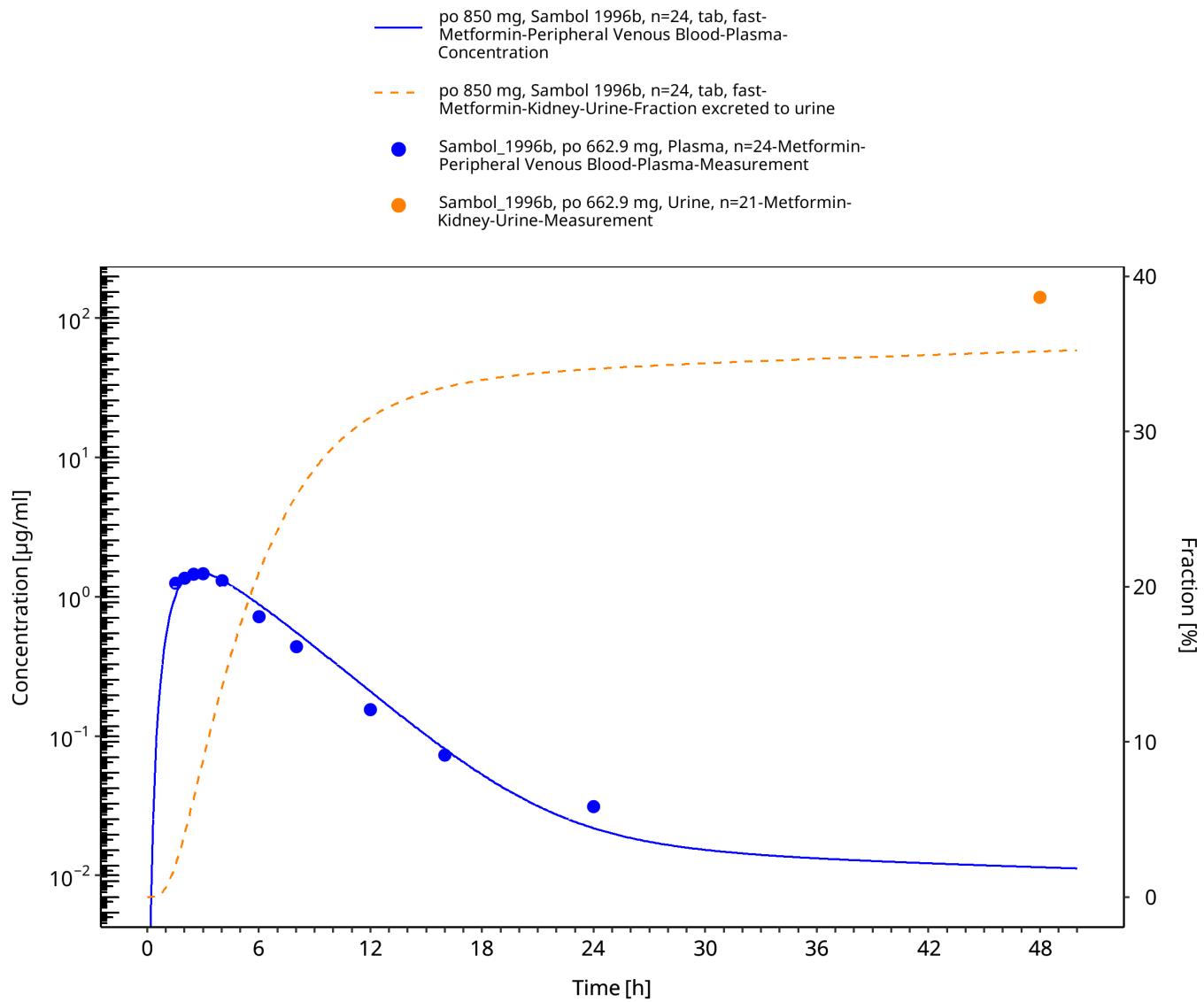


Figure 3-11: Metformin - po (tab) 850 mg_Sambol 1996b

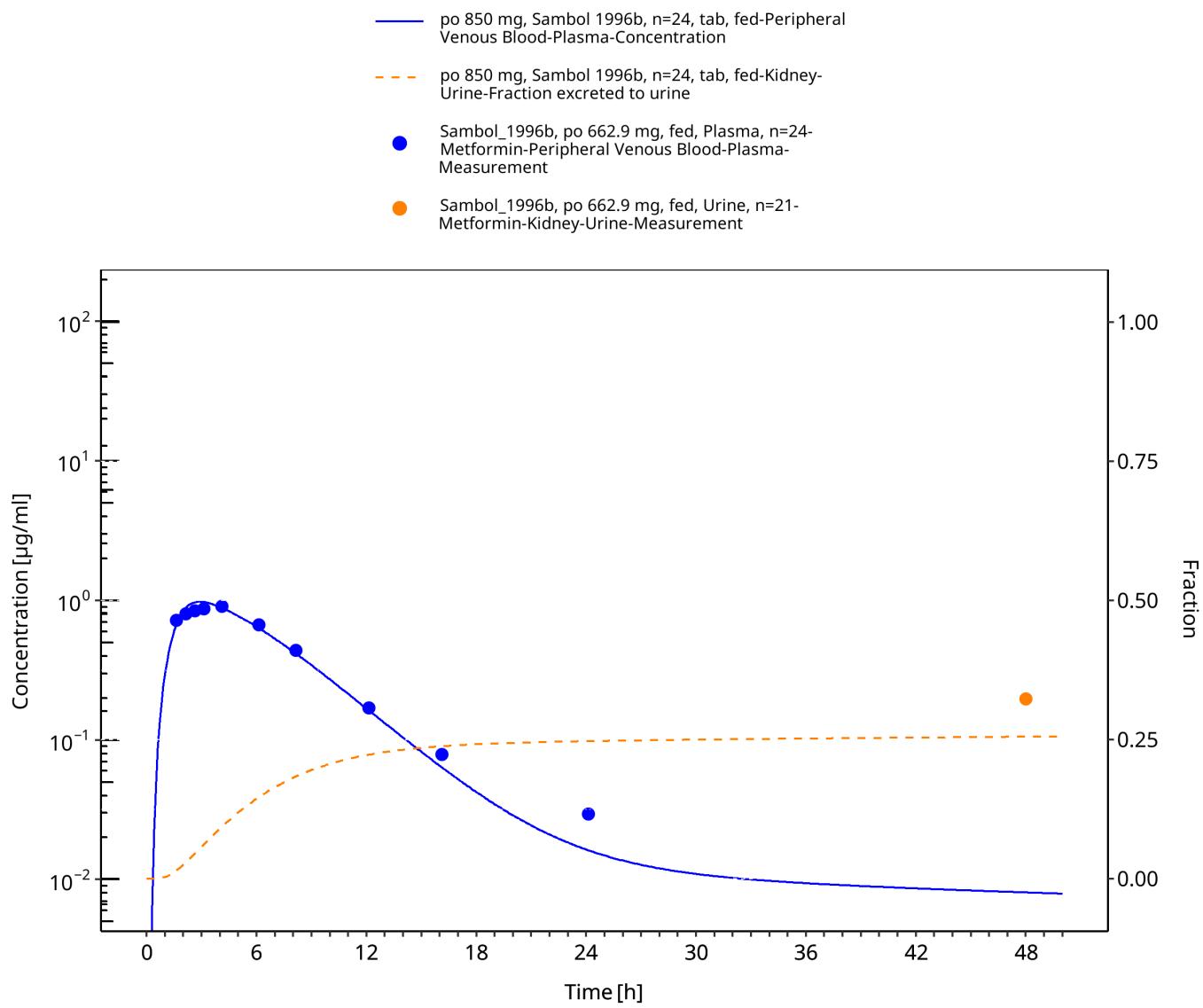


Figure 3-12: Metformin - po (tab) 850 mg_Sambol 1996a

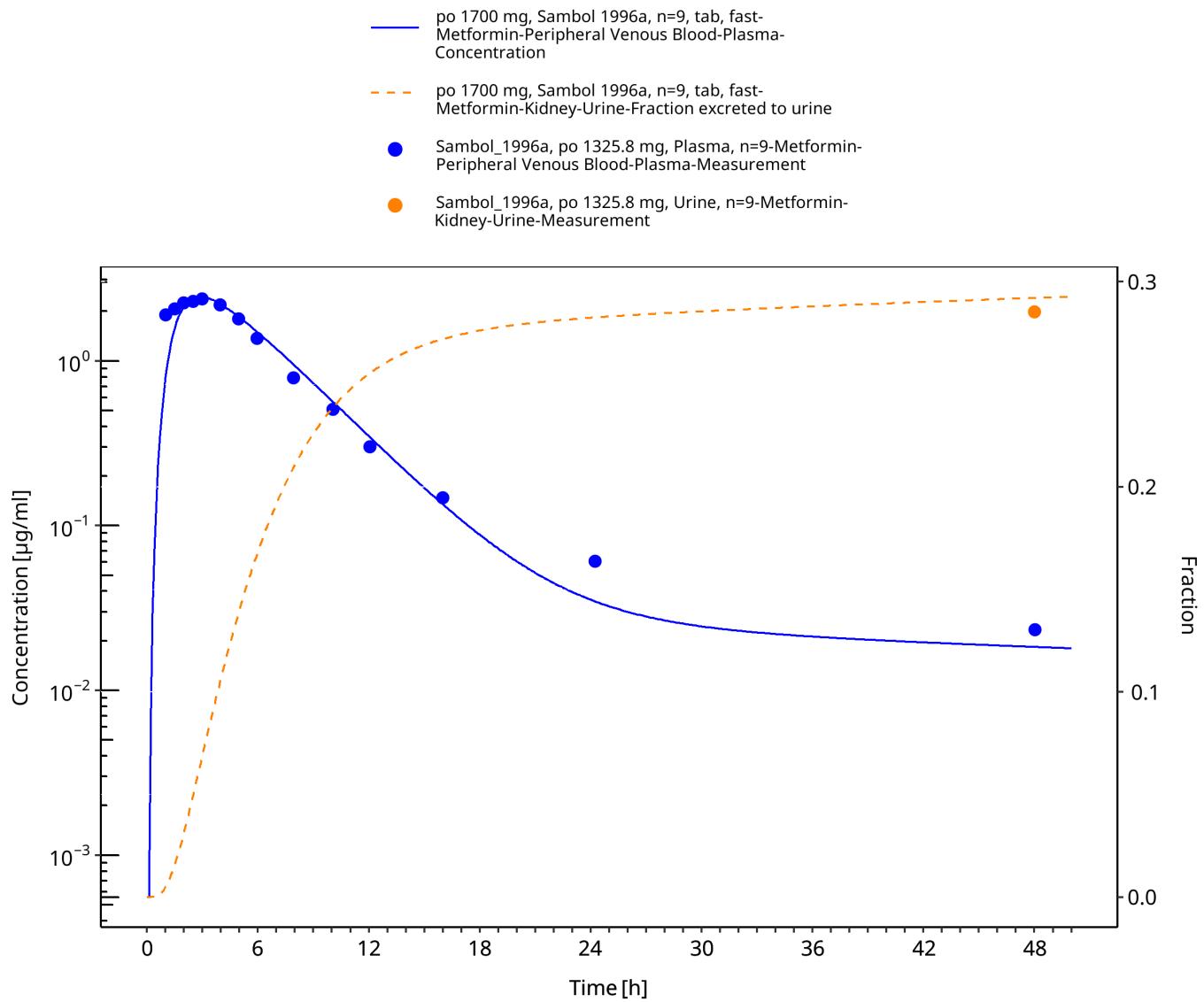


Figure 3-13: Metformin - po (tab) 0.1700 mg_Sambol 1996a

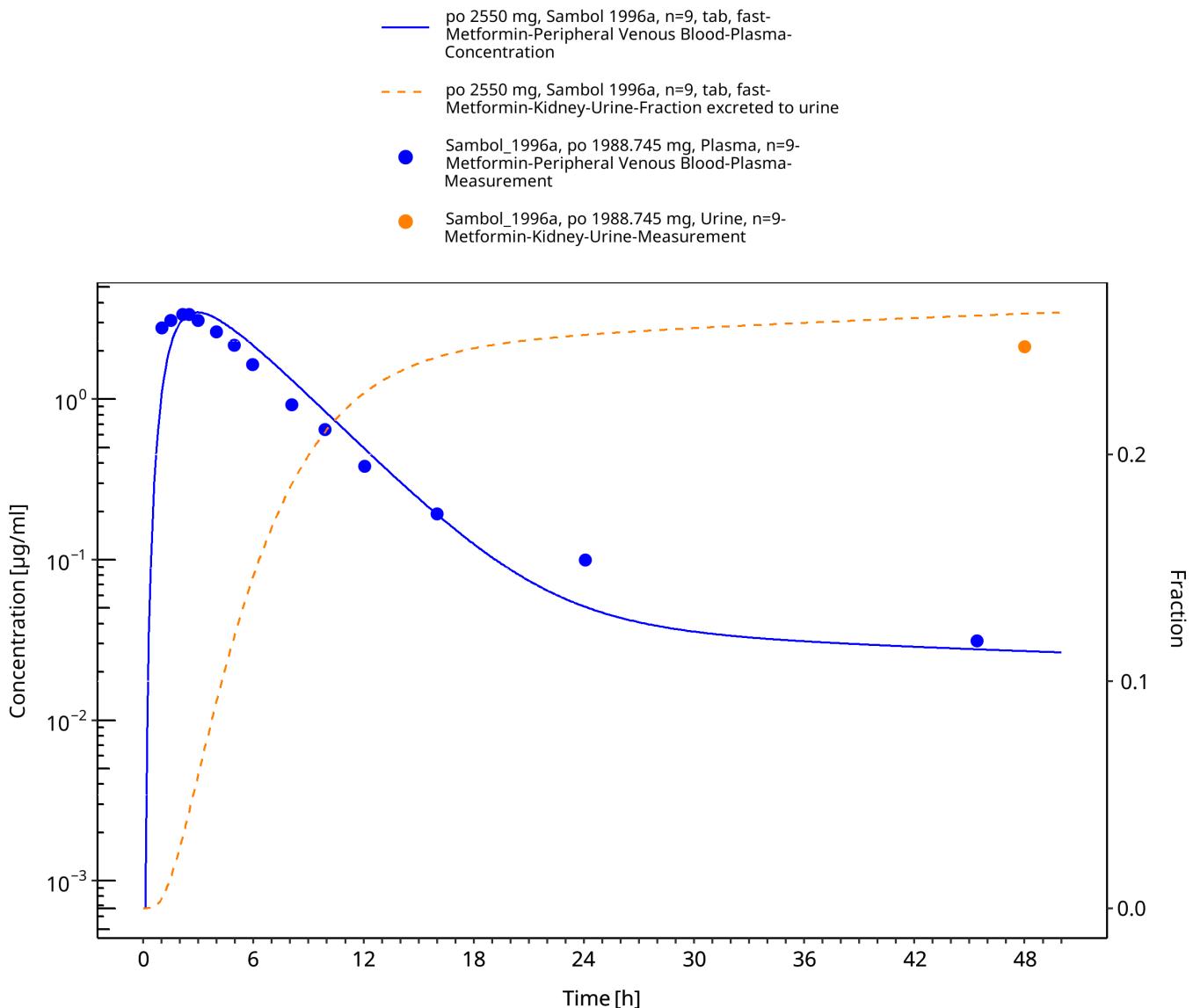


Figure 3-14: Metformin - po (tab) 2550 mg_Sambol 1996a

3.3.2 Model Verification

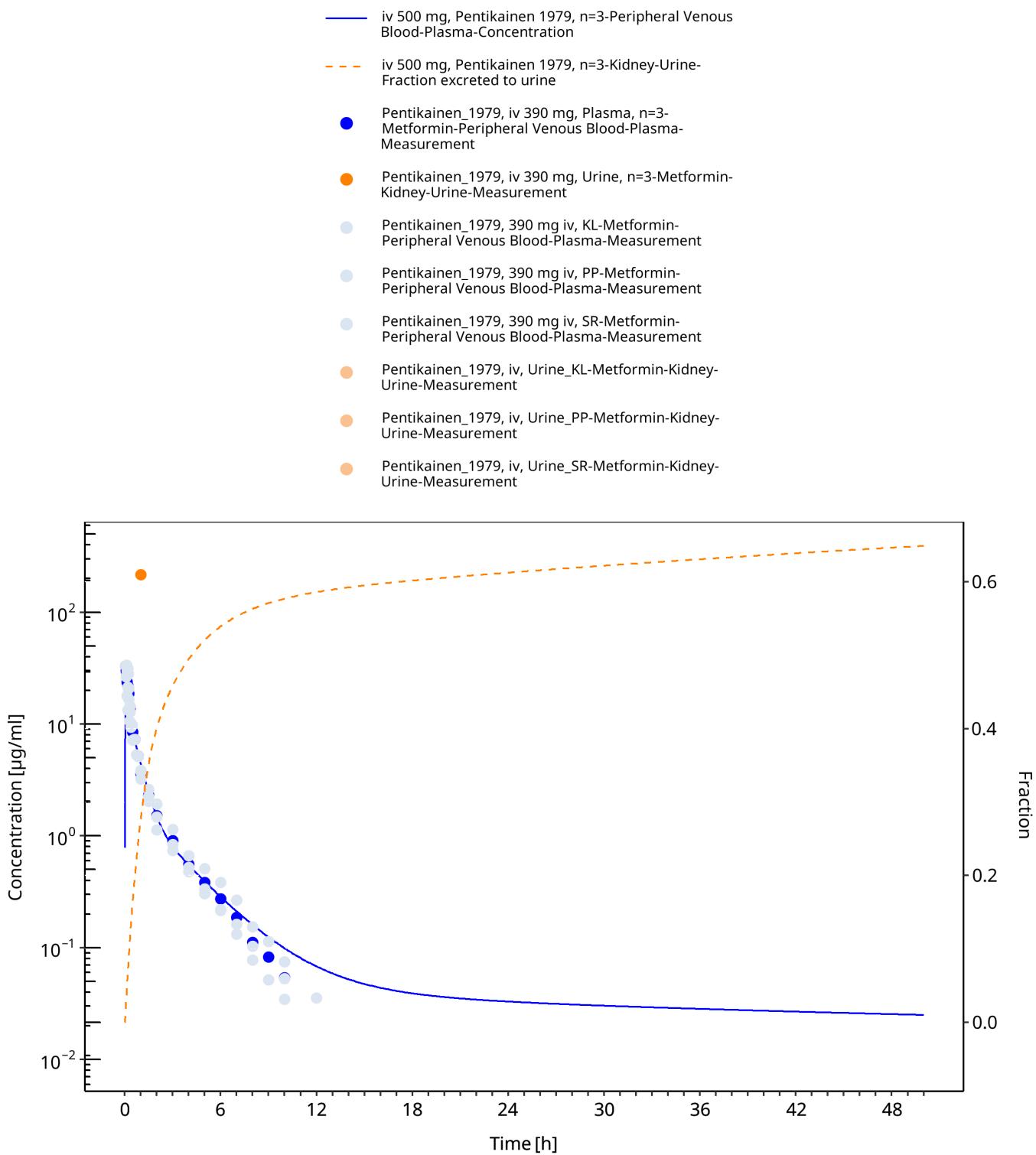


Figure 3-15: Metformin - iv 500 mg_Pentikainen 1979

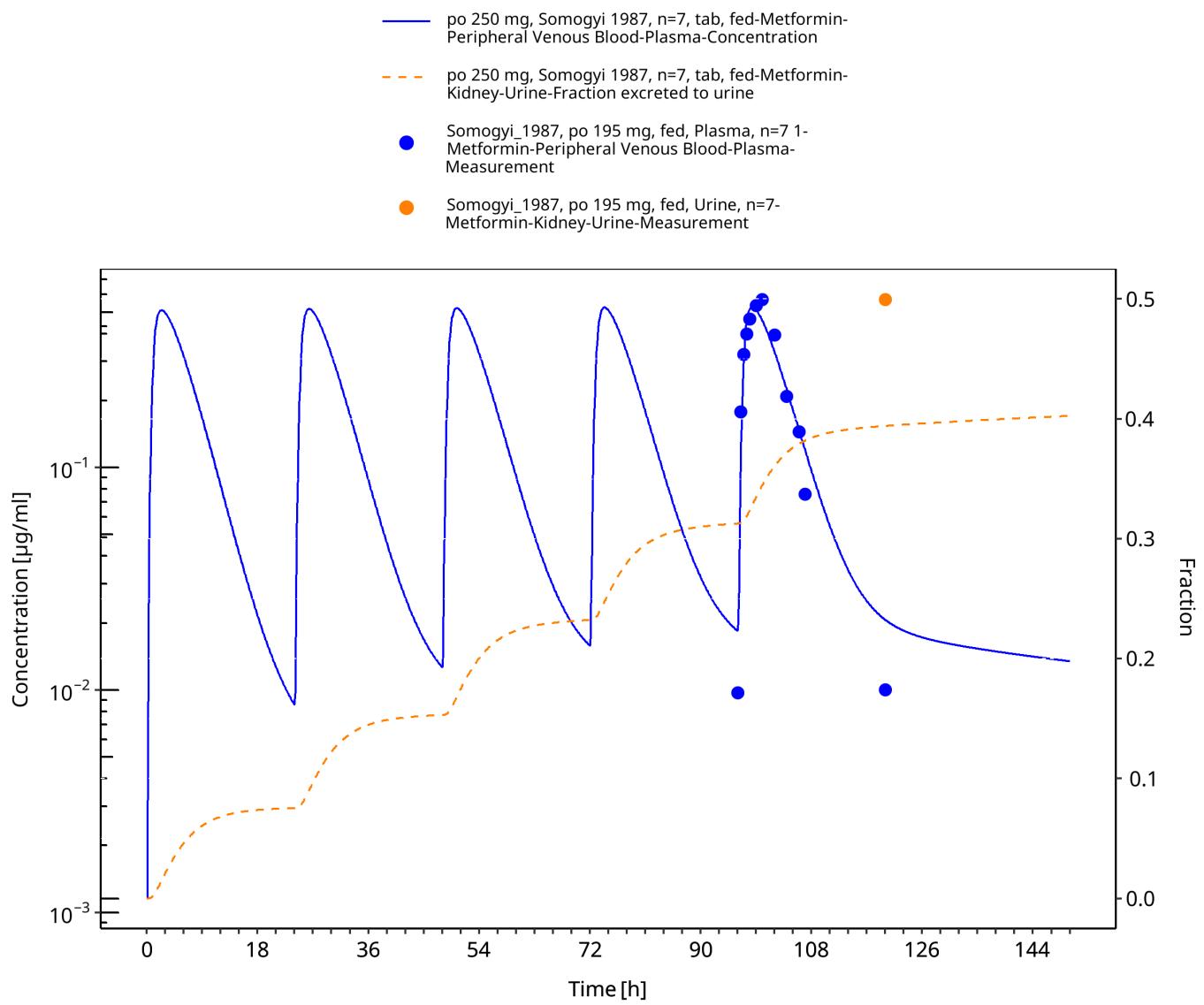


Figure 3-16: Metformin - po (tab) 250 mg_Somogyi 1987

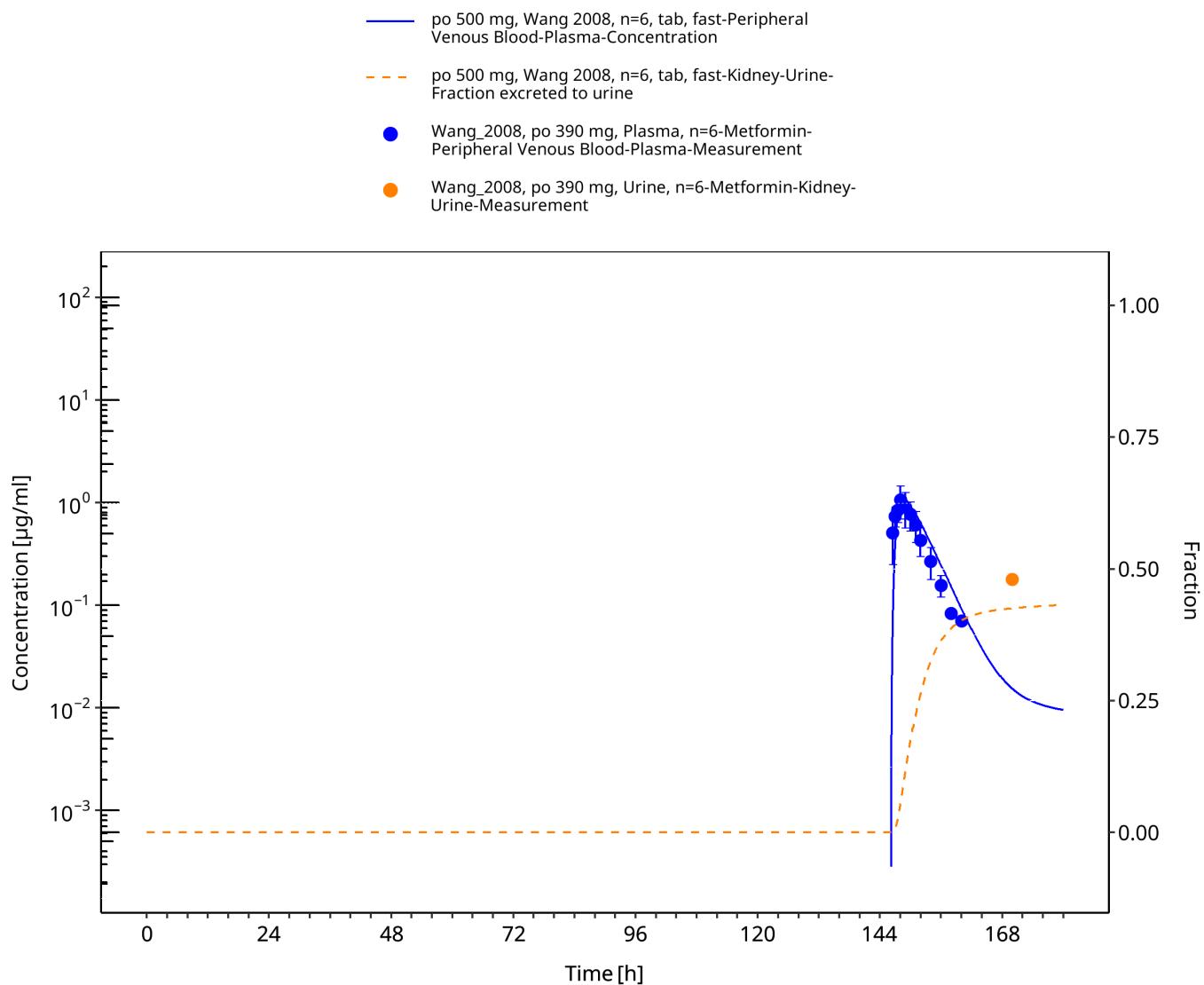


Figure 3-17: Metformin - po (tablet) 500 mg_Wang 2008

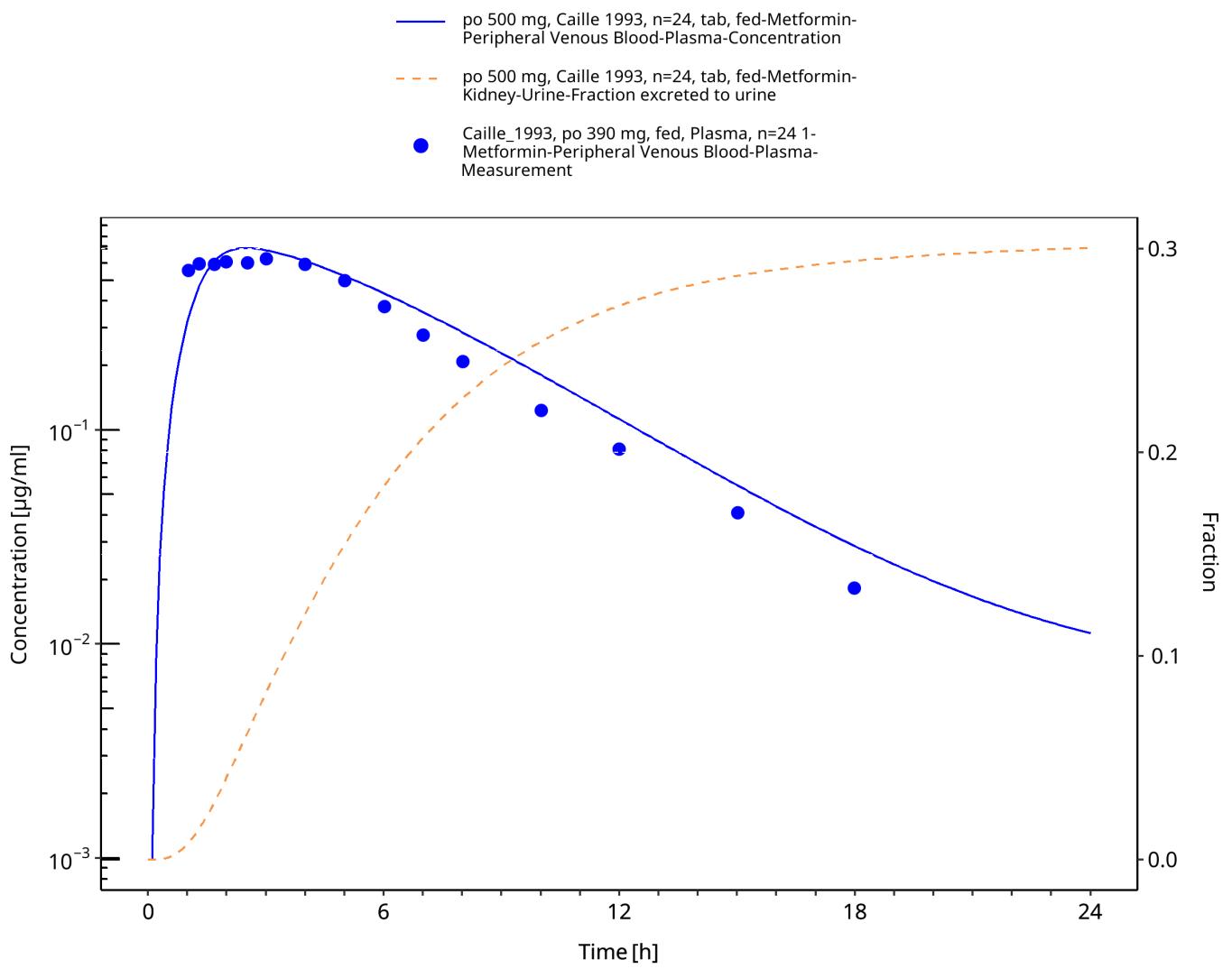


Figure 3-18: Metformin - po (tab) 500 mg_Caille 1993

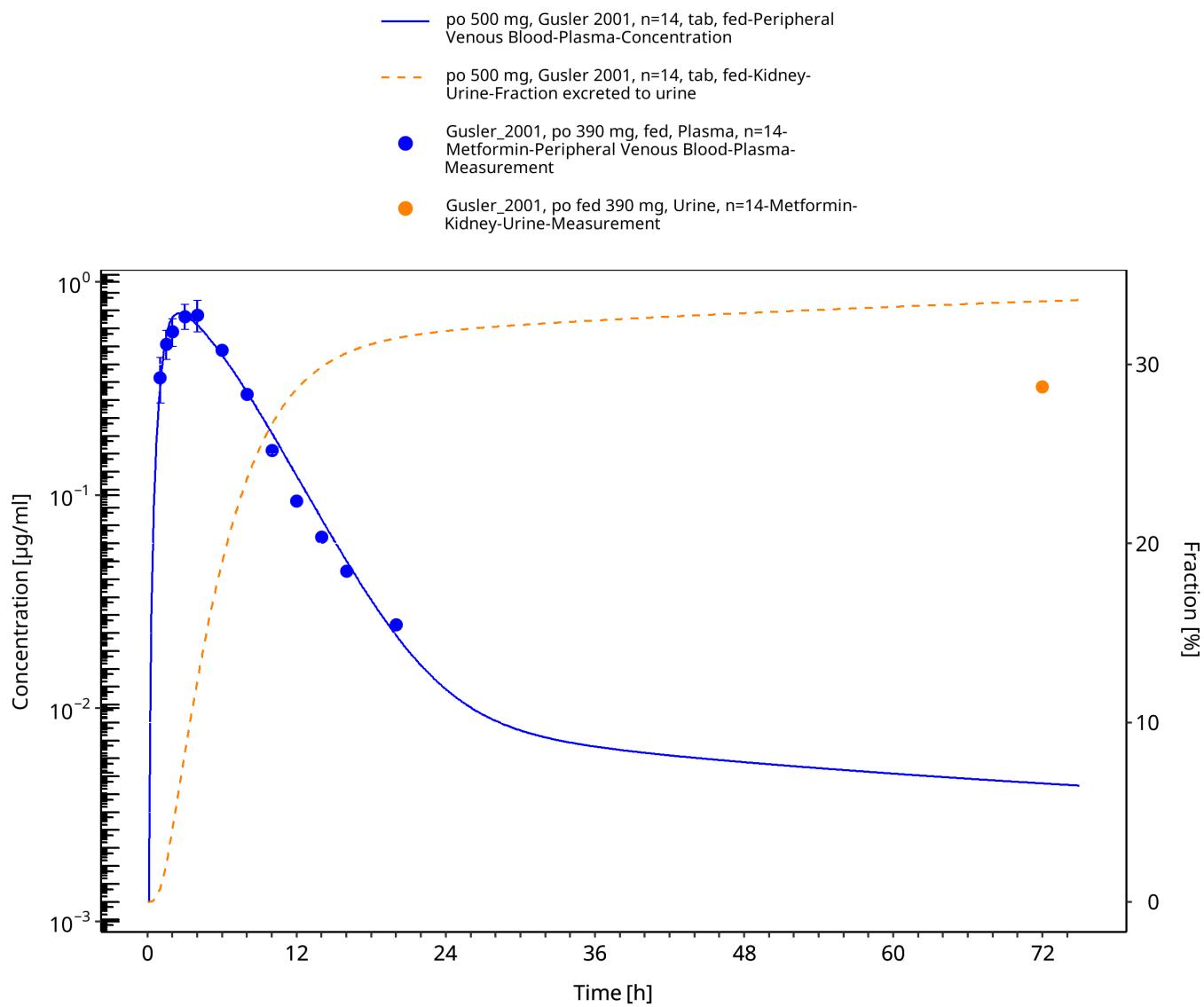


Figure 3-19: Metformin - po (tab) 500 mg_Gusler 2001

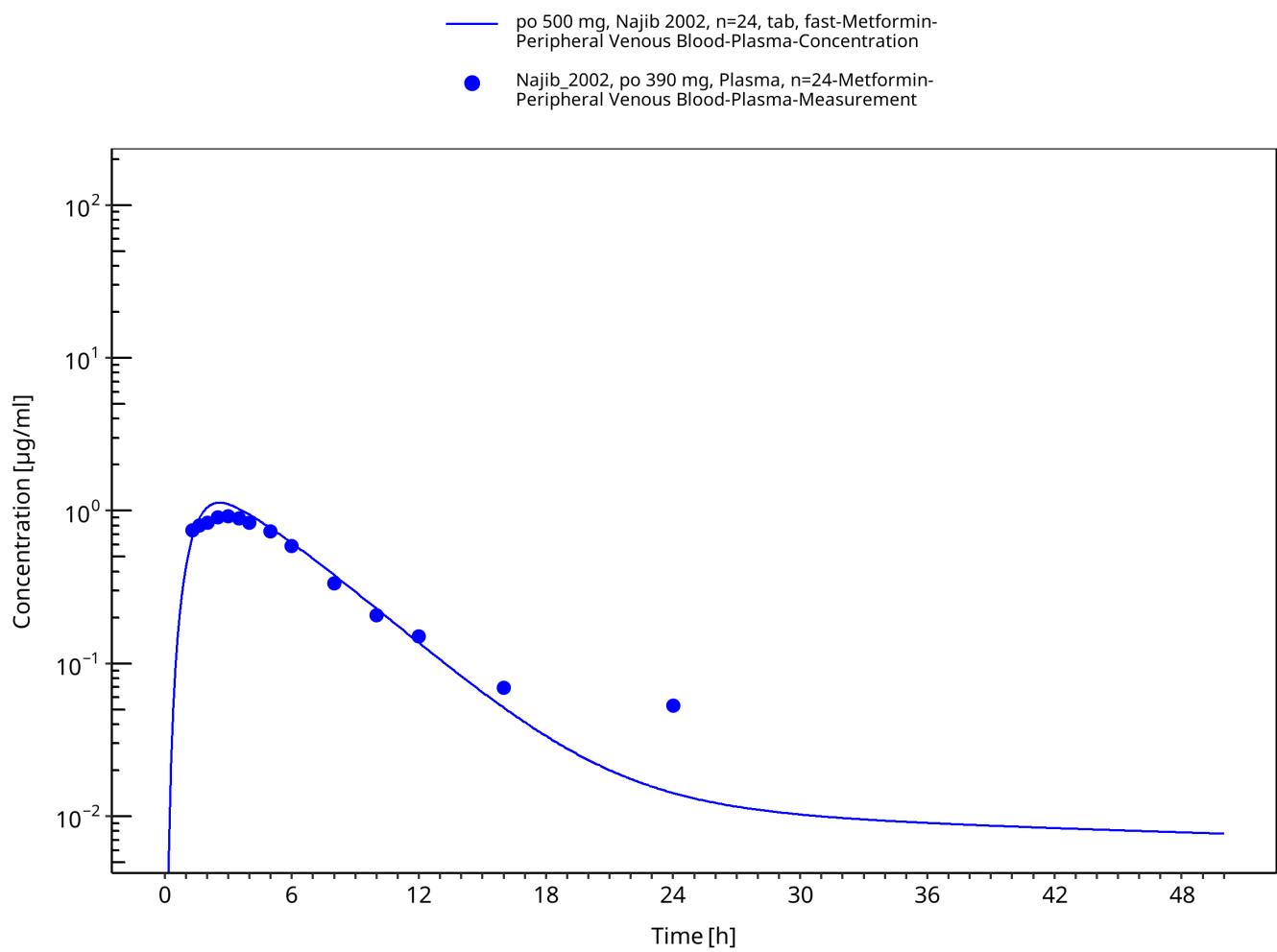


Figure 3-20: Metformin - po (tab) 500 mg_Najib 2002

- po 500 mg, Pentikainen 1979, n=5, tab, fast-Peripheral Venous Blood-Plasma-Concentration
- - - po 500 mg, Pentikainen 1979, n=5, tab, fast-Kidney-Urine-Fraction excreted to urine
- Pentikainen_1979, po, Urine_KL-Metformin-Kidney-Urine-Measurement
- Pentikainen_1979, po, Urine_PP-Metformin-Kidney-Urine-Measurement
- Pentikainen_1979, po, Urine_RL-Metformin-Kidney-Urine-Measurement
- Pentikainen_1979, po, Urine_SR-Metformin-Kidney-Urine-Measurement
- Pentikainen_1979, po, Urine_TK-Metformin-Kidney-Urine-Measurement
- Pentikainen_1979, 390 mg po, TK-Metformin-Peripheral Venous Blood-Plasma-Measurement
- Pentikainen_1979, 390 mg po, SR-Metformin-Peripheral Venous Blood-Plasma-Measurement
- Pentikainen_1979, 390 mg po, RL-Metformin-Peripheral Venous Blood-Plasma-Measurement
- Pentikainen_1979, 390 mg po, PP-Metformin-Peripheral Venous Blood-Plasma-Measurement
- Pentikainen_1979, 390 mg po, KL-Metformin-Peripheral Venous Blood-Plasma-Measurement
- Pentikainen_1979, po 390 mg, Urine, n=5-Metformin-Kidney-Urine-Measurement
- Pentikainen_1979, po 390 mg, Plasma, n=5-Metformin-Peripheral Venous Blood-Plasma-Measurement

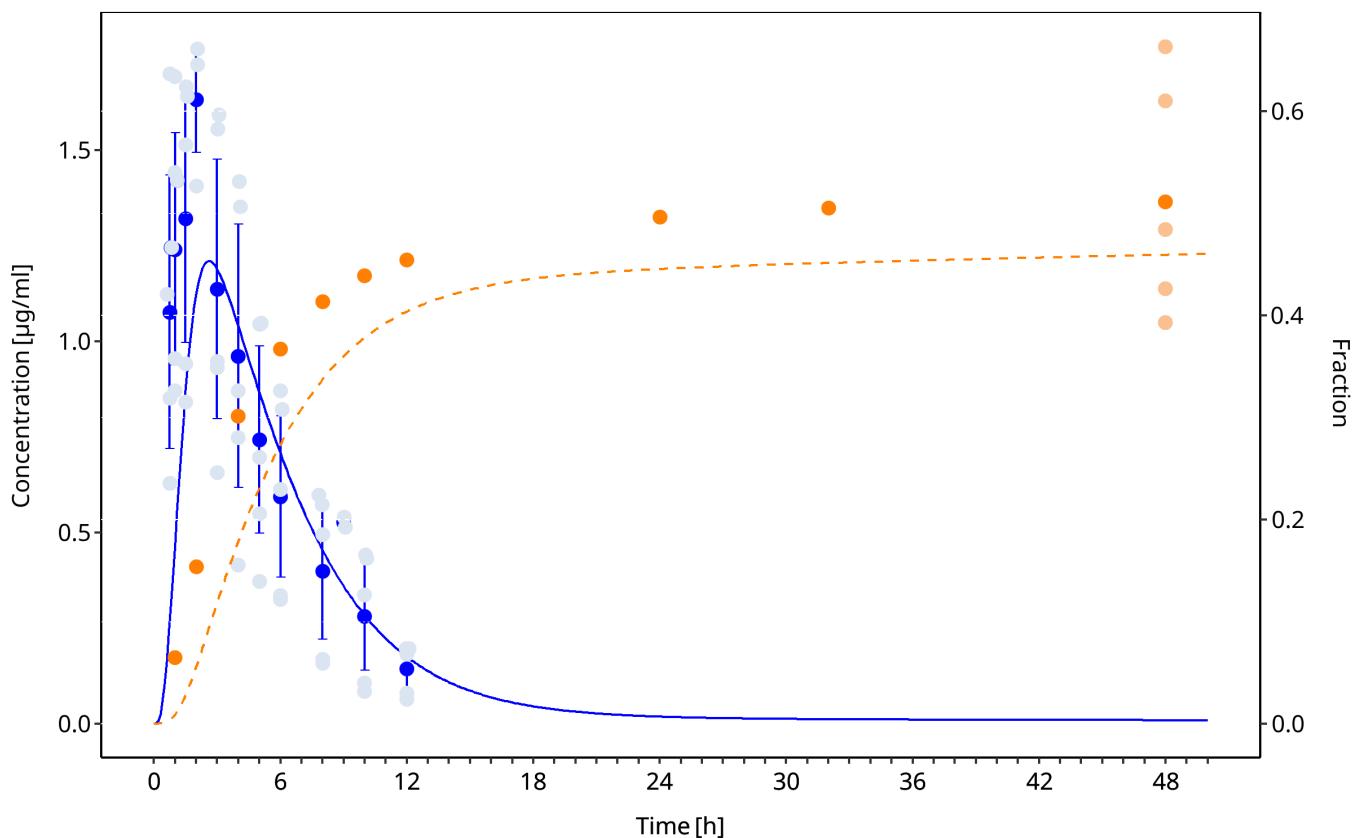


Figure 3-21: Metformin - po (tab) 500 mg_Pentikainen 1979

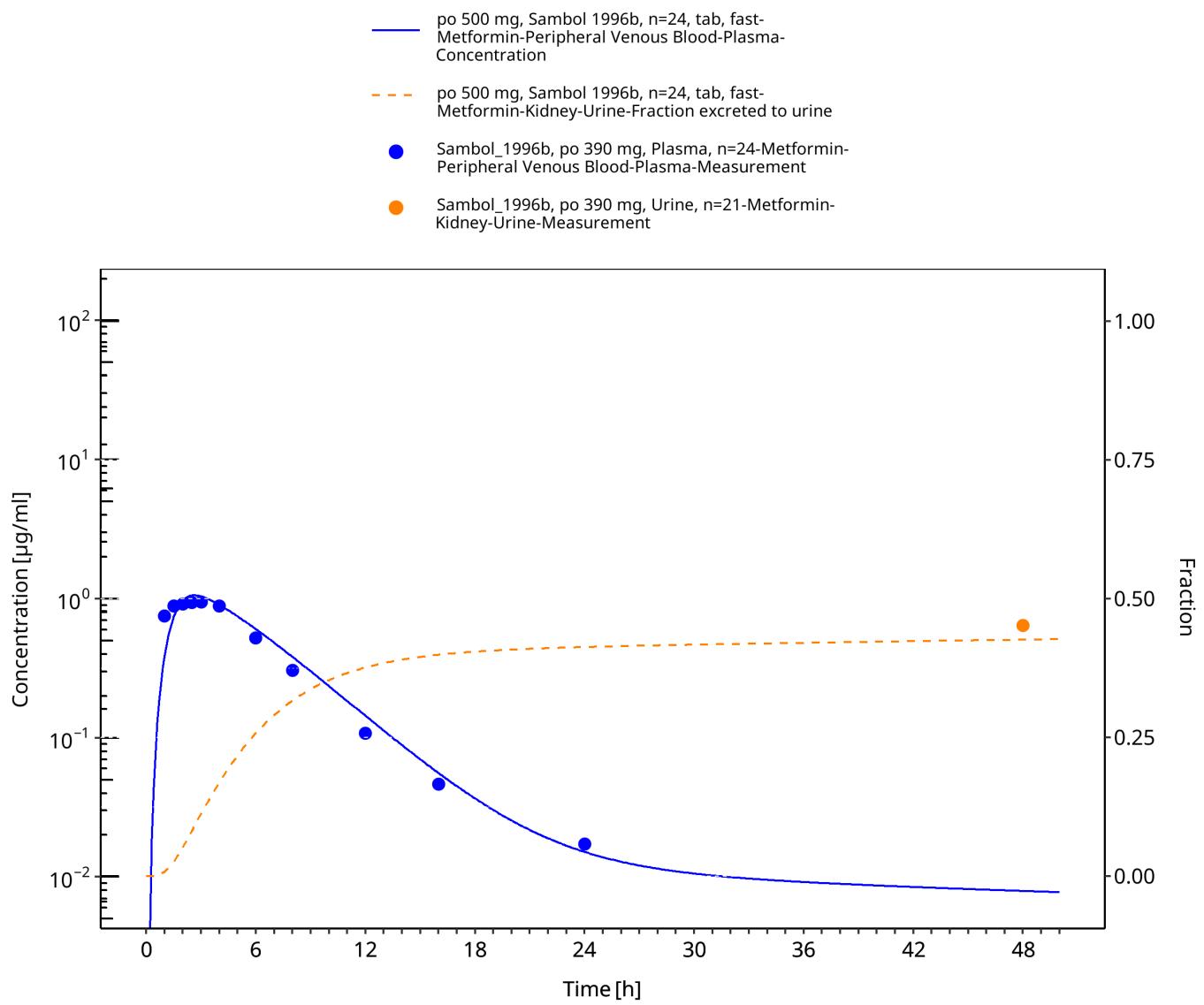


Figure 3-22: Metformin - po (tab) 500 mg_Sambol 1996b

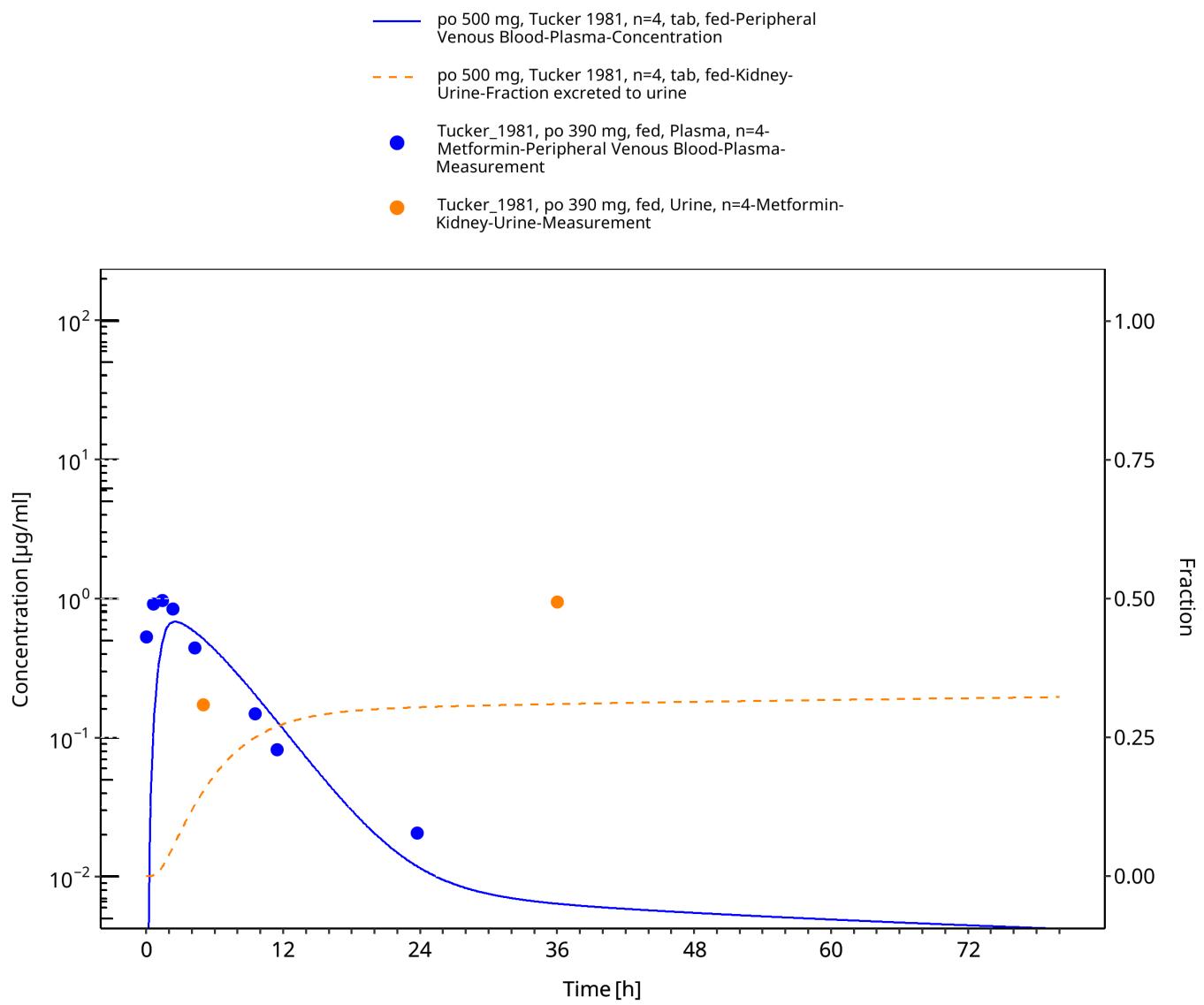


Figure 3-23: Metformin - po (tab) 500 mg_Tucker 1981

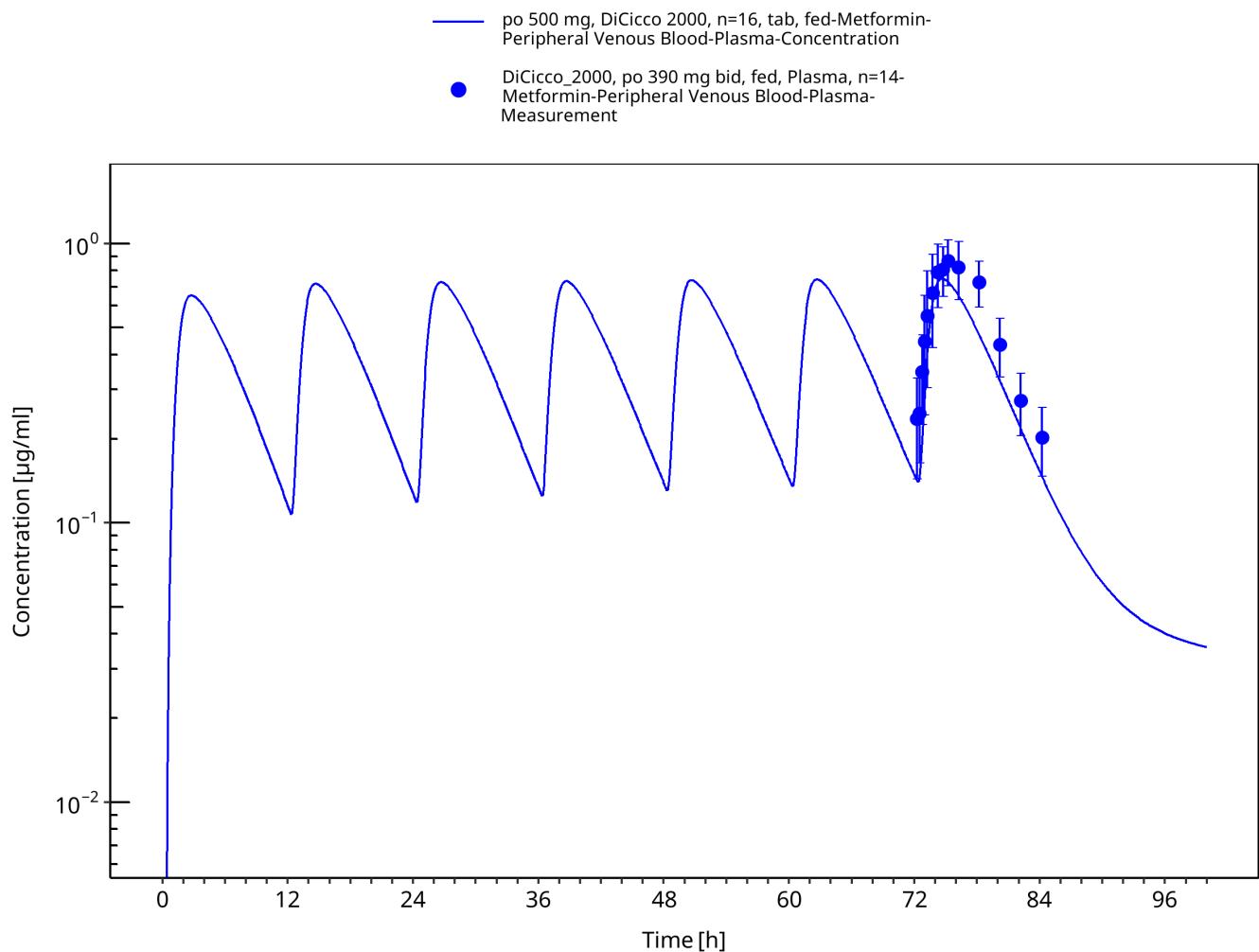


Figure 3-24: Metformin - po (tab) 500 mg_DiCicco 2000

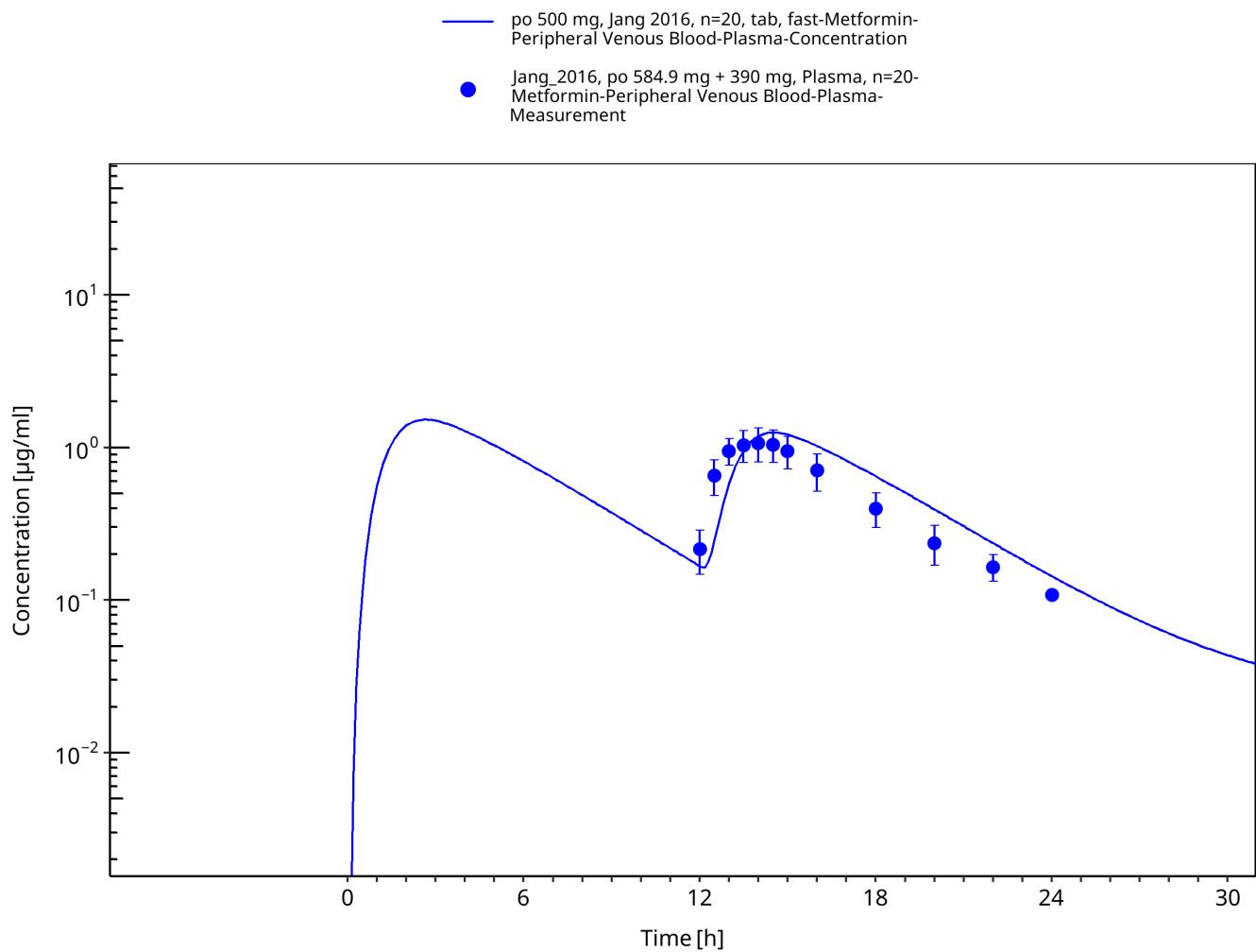


Figure 3-25: Metformin - po (tab) 500 mg_Jan 2016

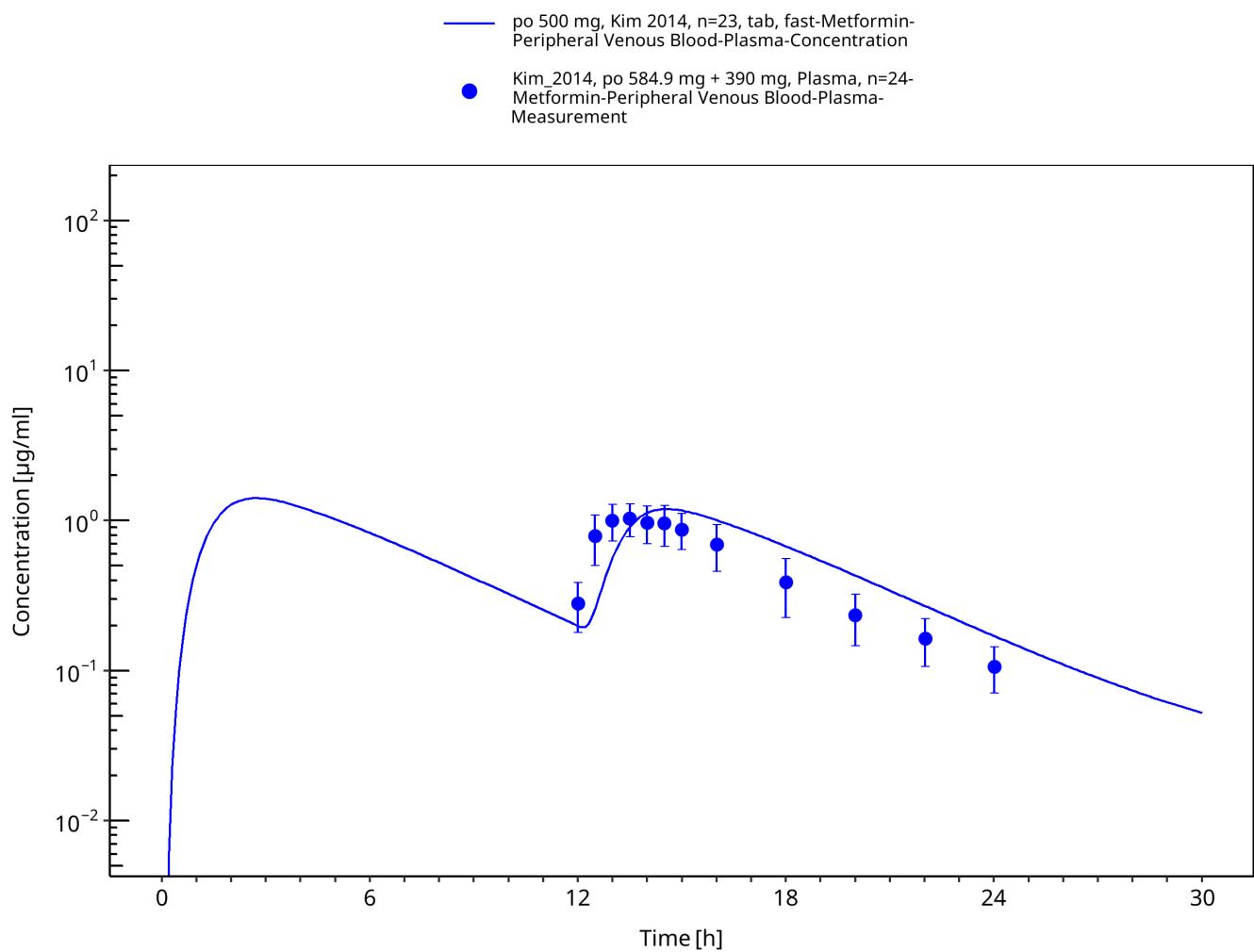


Figure 3-26: Metformin - po (tab) 500 mg_Kim 2014

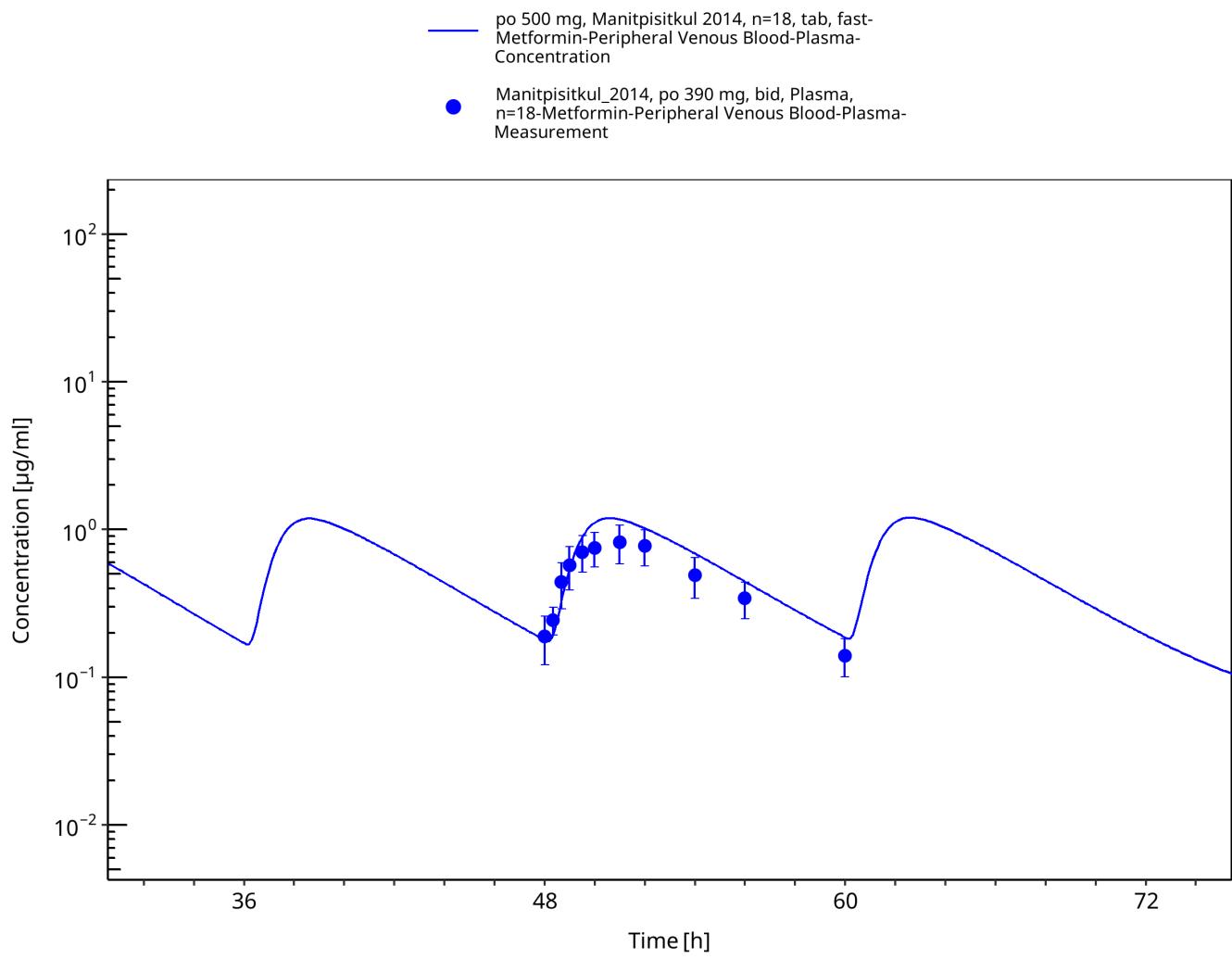


Figure 3-27: Metformin - po (tab) 500 mg_Manitpisitkul 2014

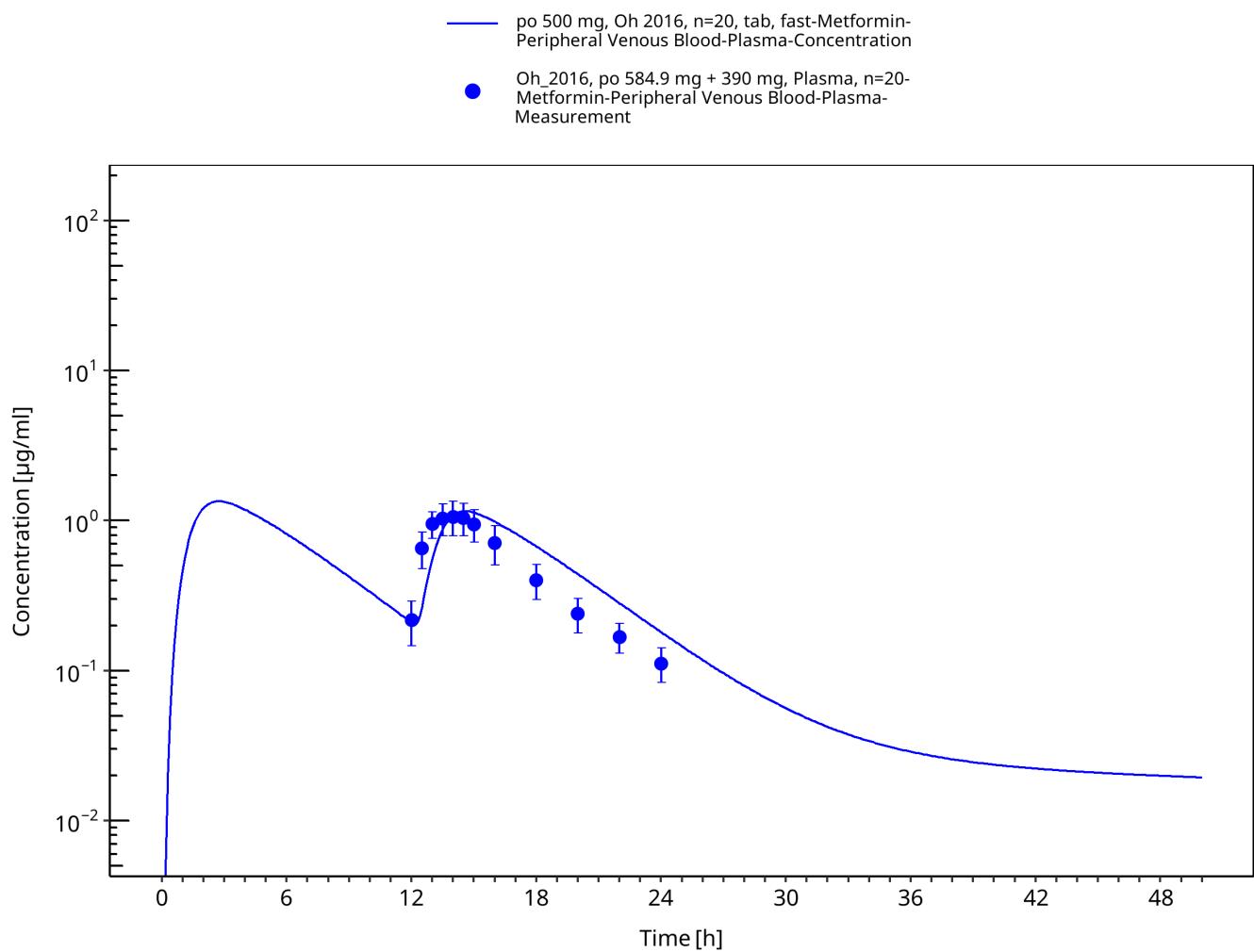


Figure 3-28: Metformin - po (tab) 500 mg_Oh 2016

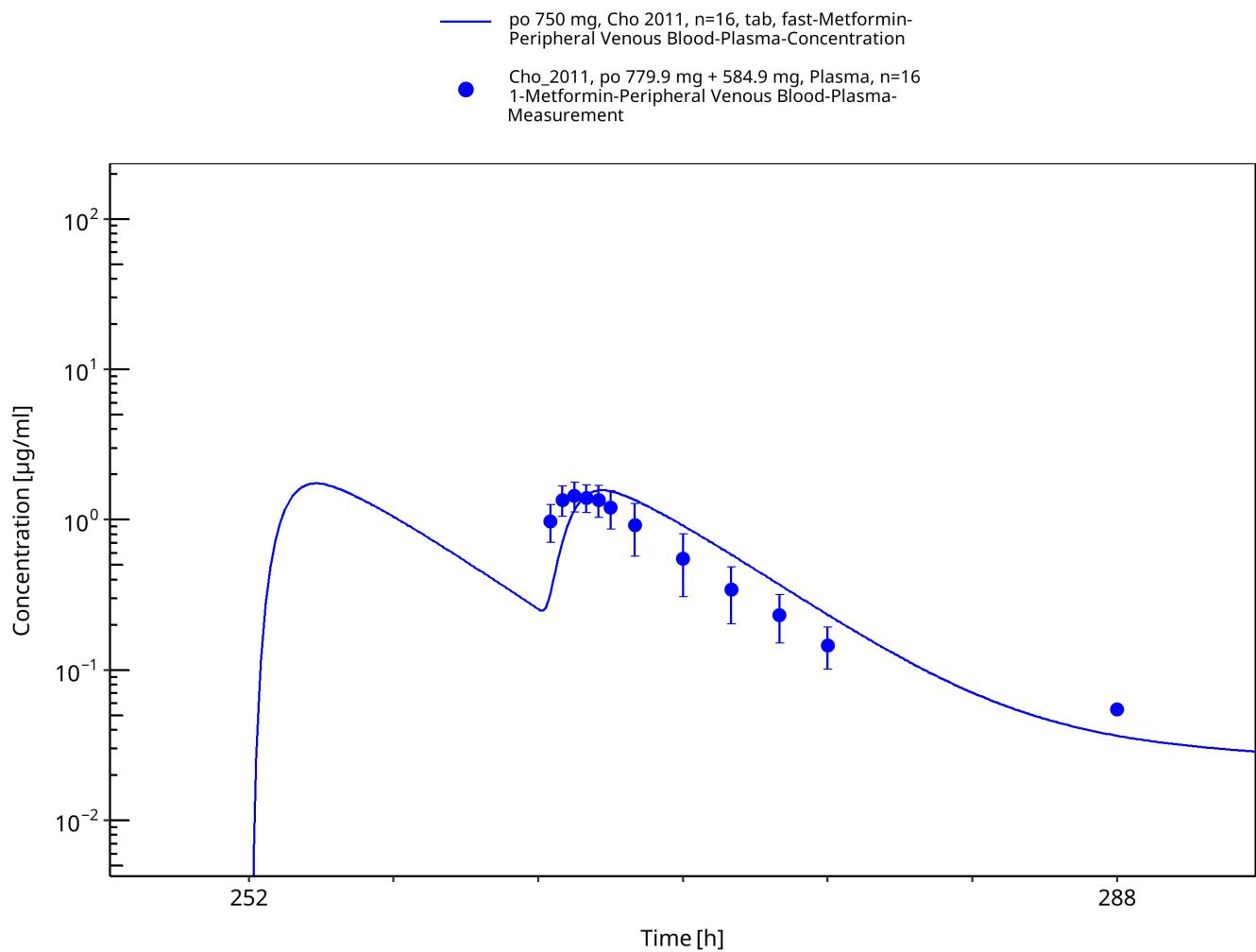


Figure 3-29: Metformin - po (tab) 750 mg_Cho 2011

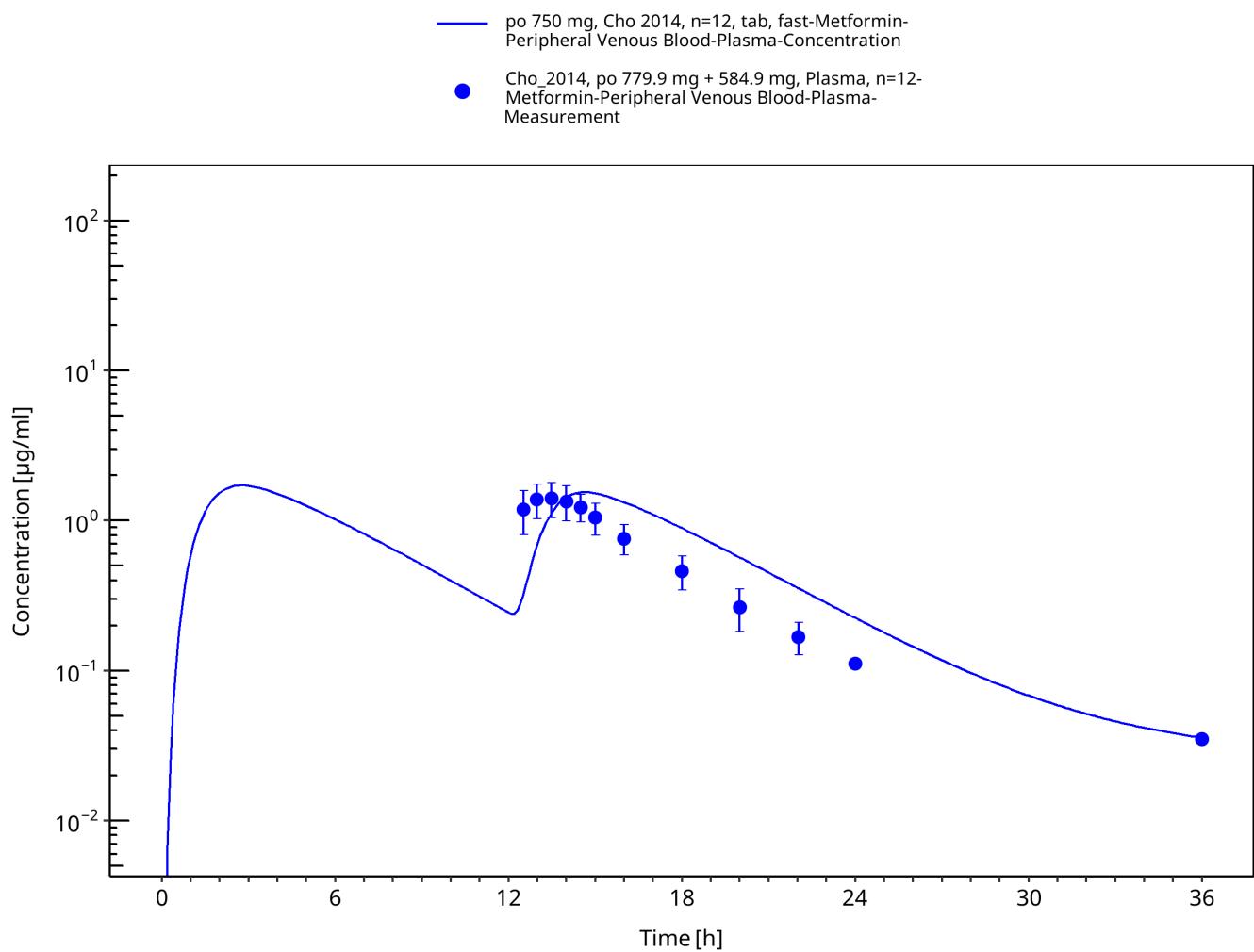


Figure 3-30: Metformin - po (tab) 750 mg_Cho 2014

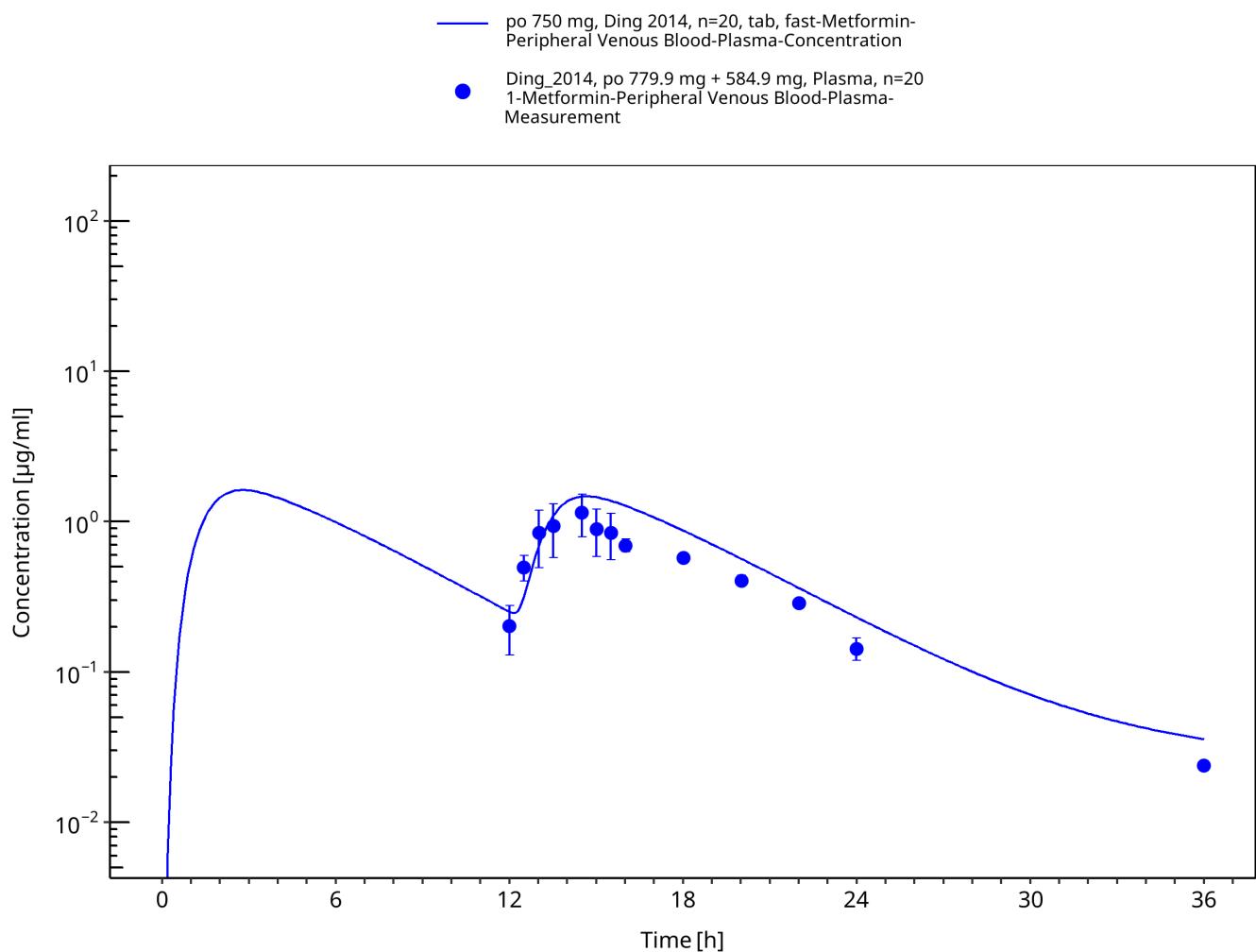


Figure 3-31: Metformin - po (tab) 750 mg tid_Ding 2014

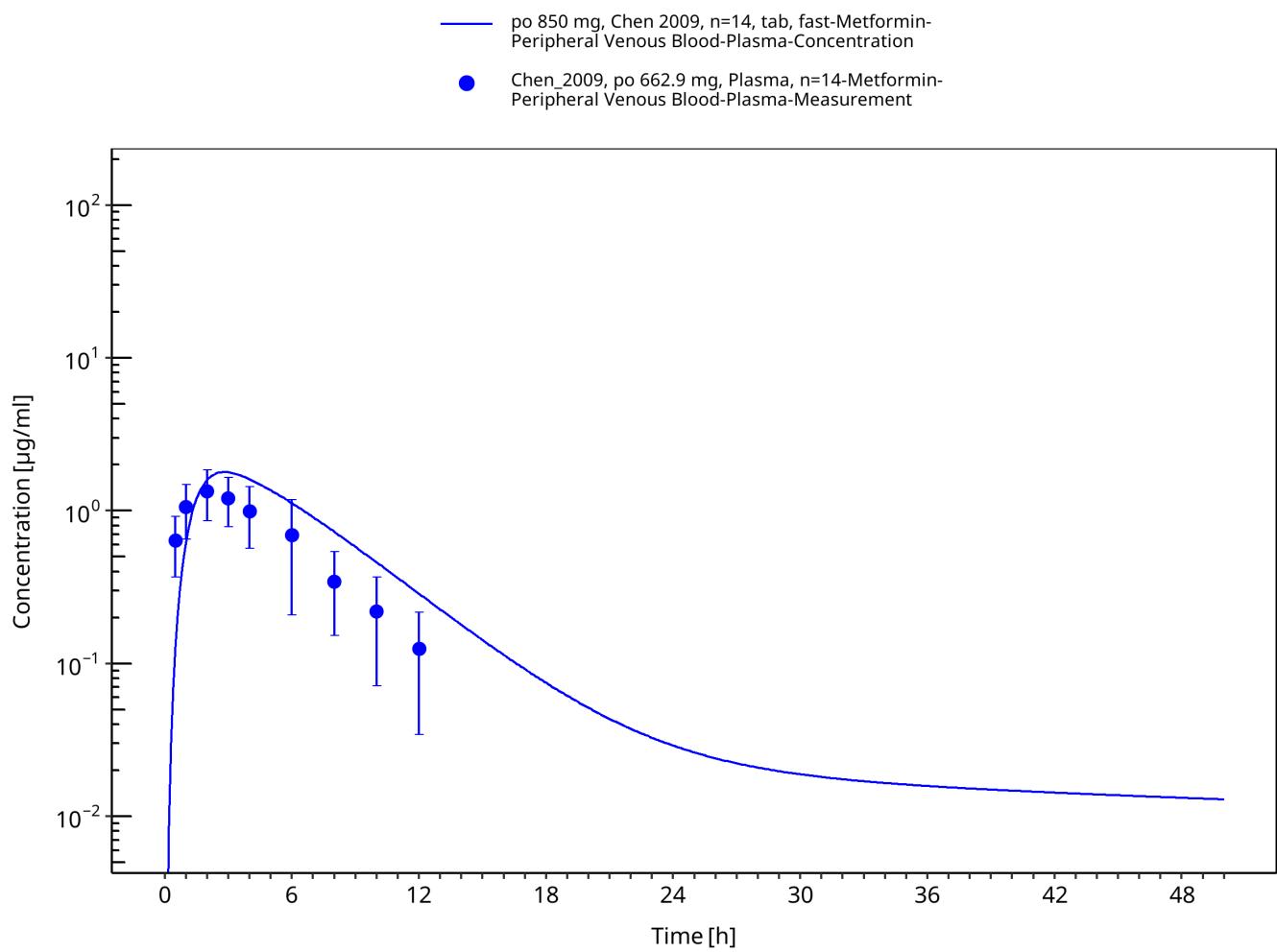


Figure 3-32: Metformin - po (tab) 850 mg_Chen 2009

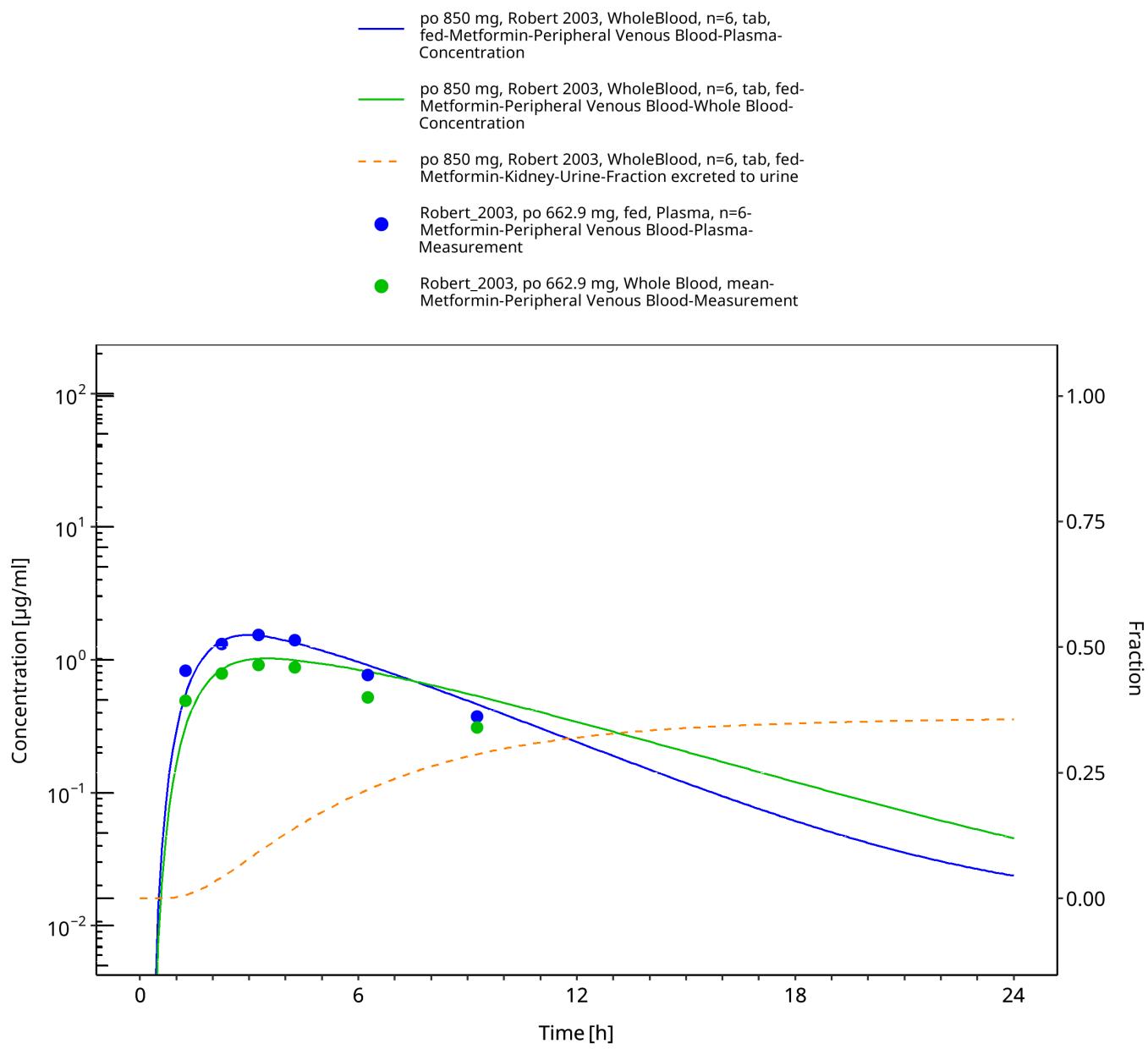


Figure 3-33: Metformin - po (tab) 850 mg_Robert 2003

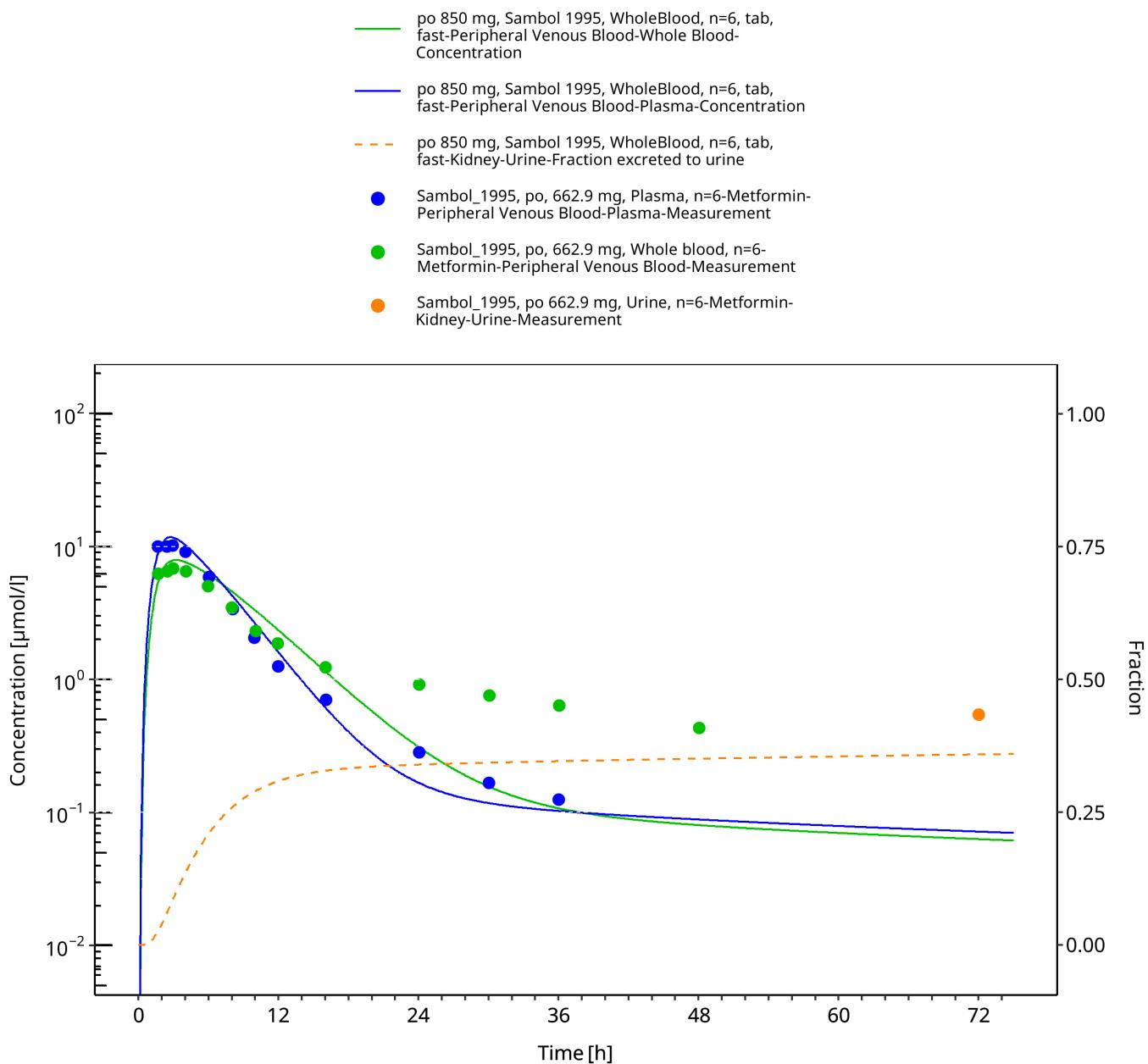


Figure 3-34: Metformin - po (tab) 850 mg_Sambol 1995

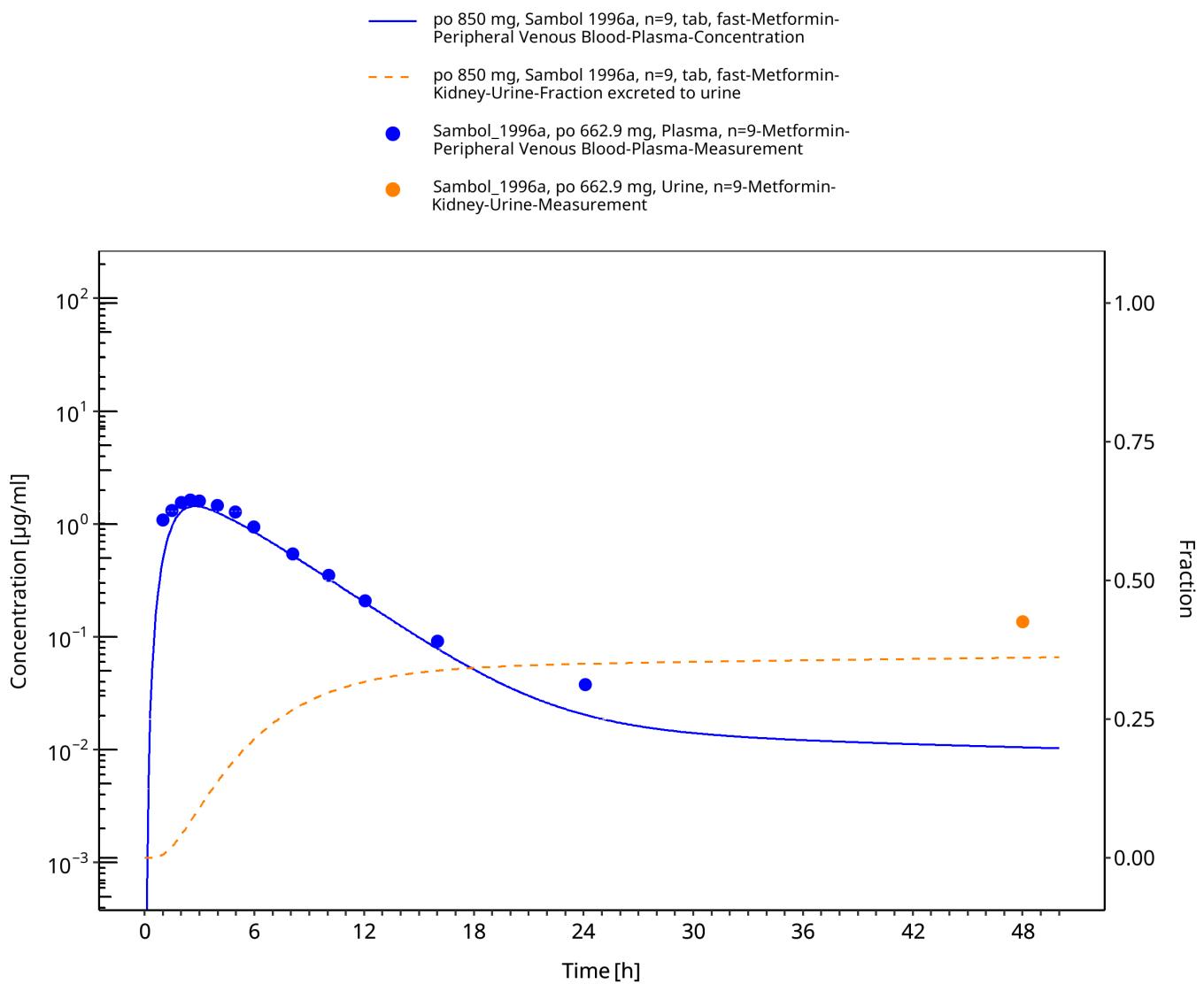


Figure 3-35: Metformin - po (tab) 850 mg_Sambol 1996a

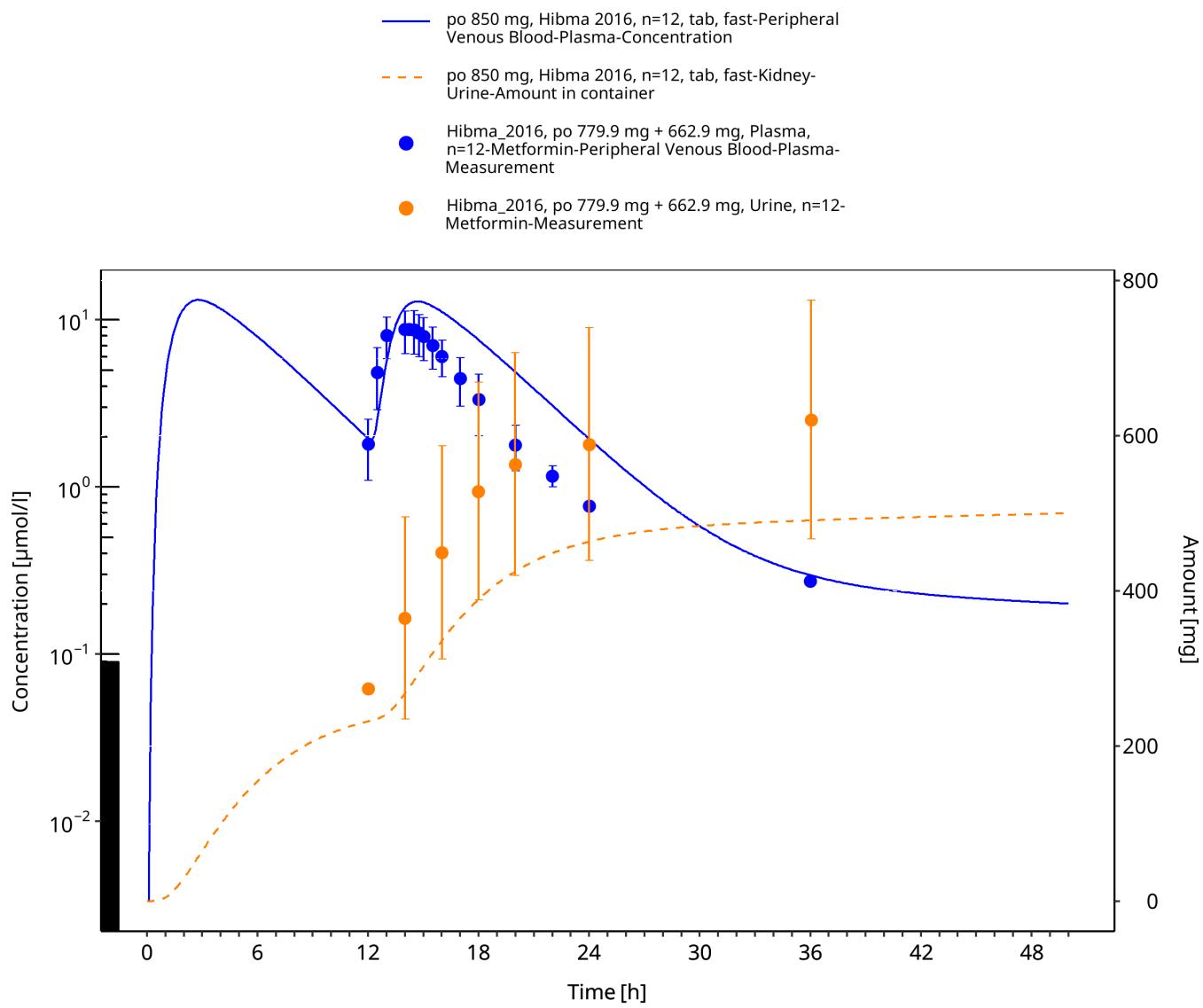


Figure 3-36: Metformin - po (tab) 850 mg_Hibma 2016

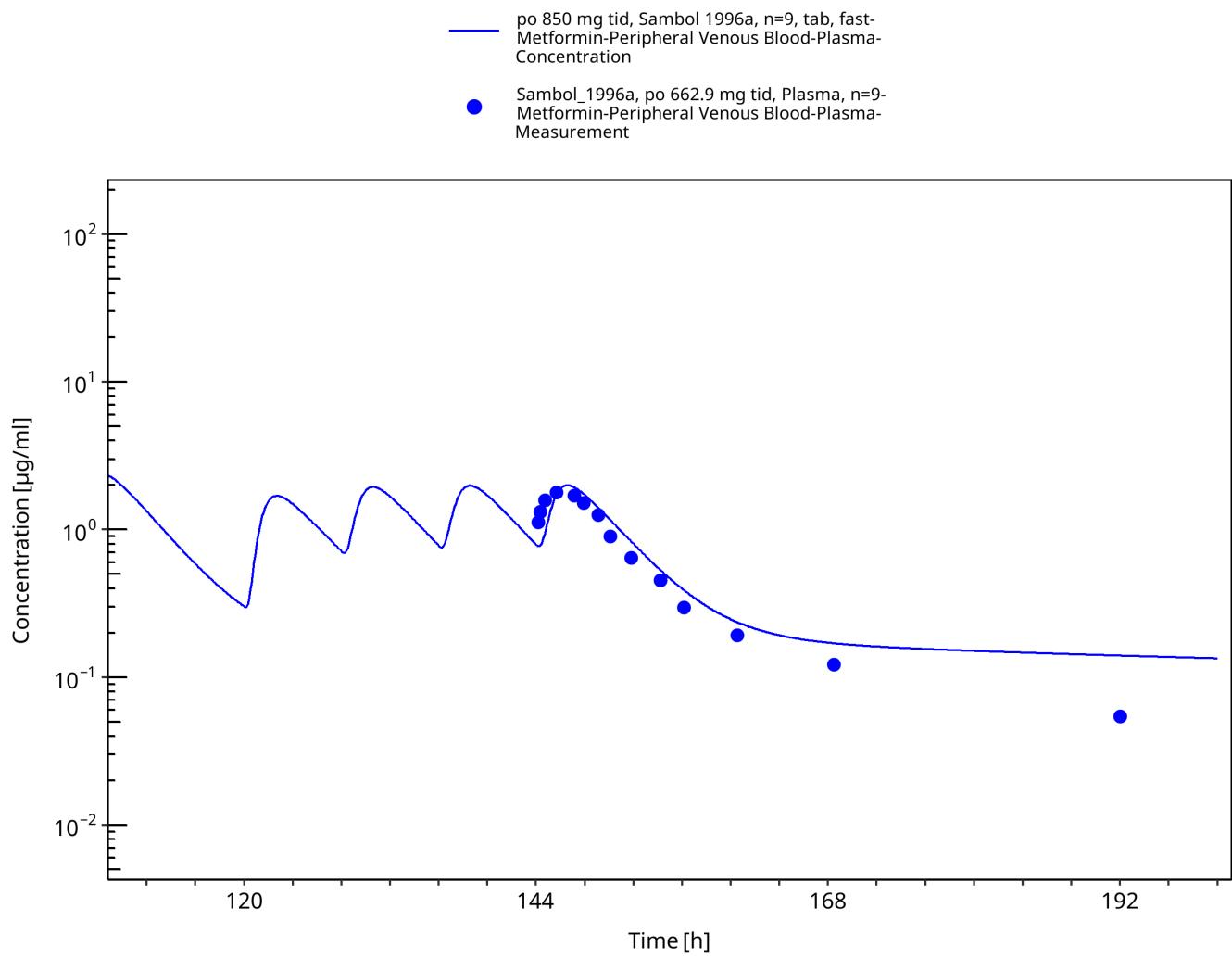


Figure 3-37: Metformin - po (tab) 850 mg tid_Sambol 1996a

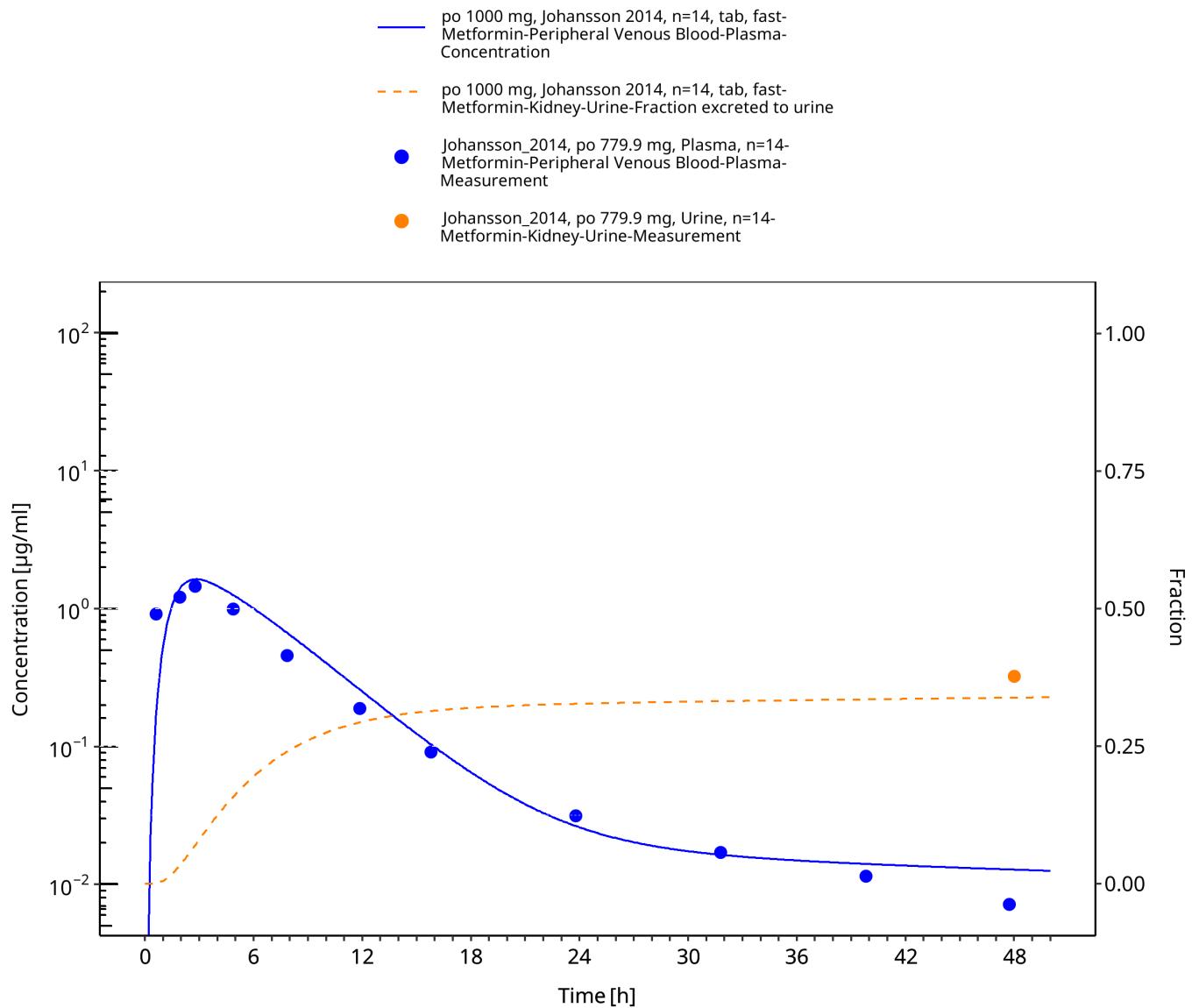


Figure 3-38: Metformin - po (tab) 1000 mg_Johansson 2014

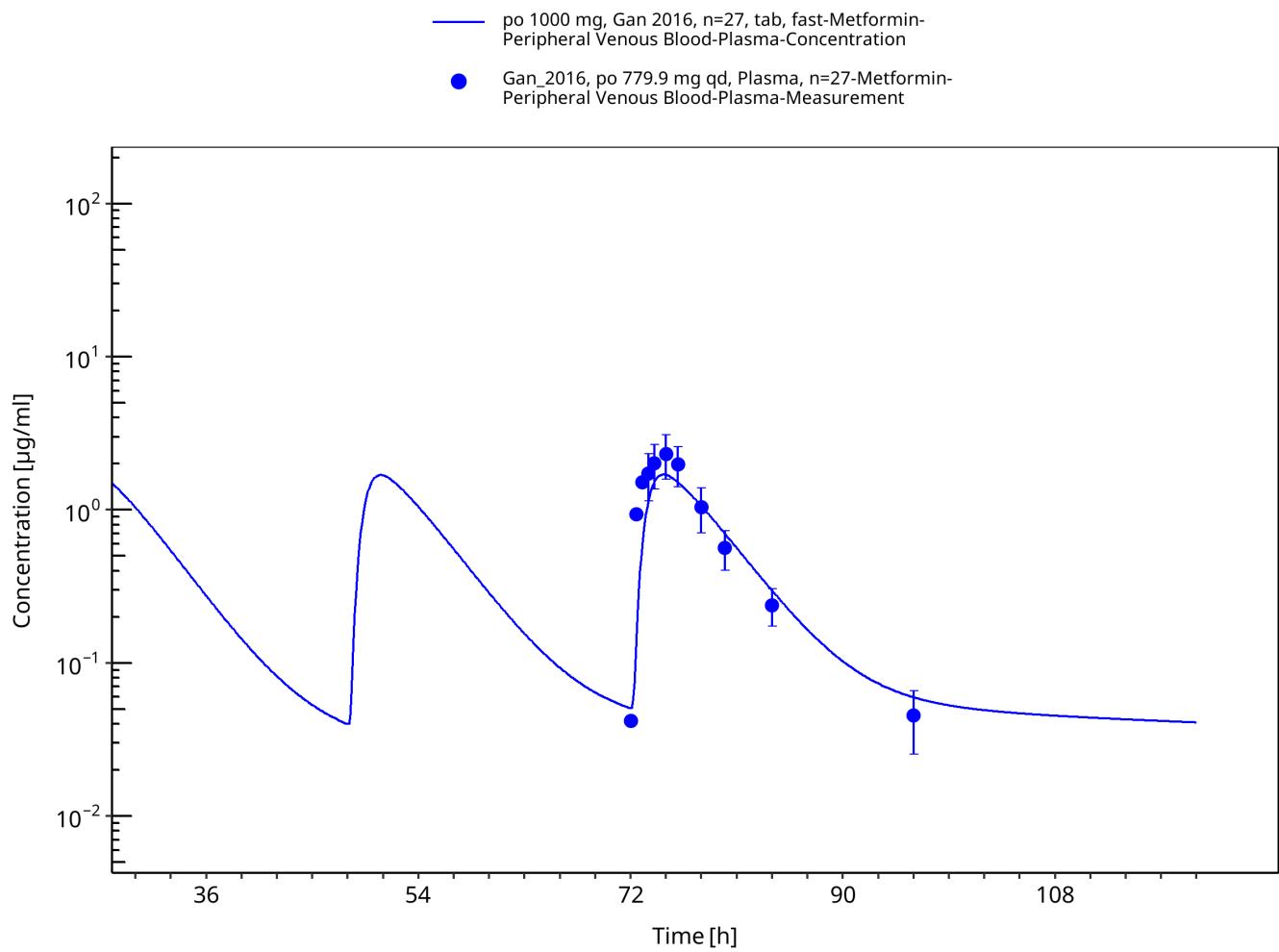


Figure 3-39: Metformin - po (tab) 1000 mg_Gan 2016

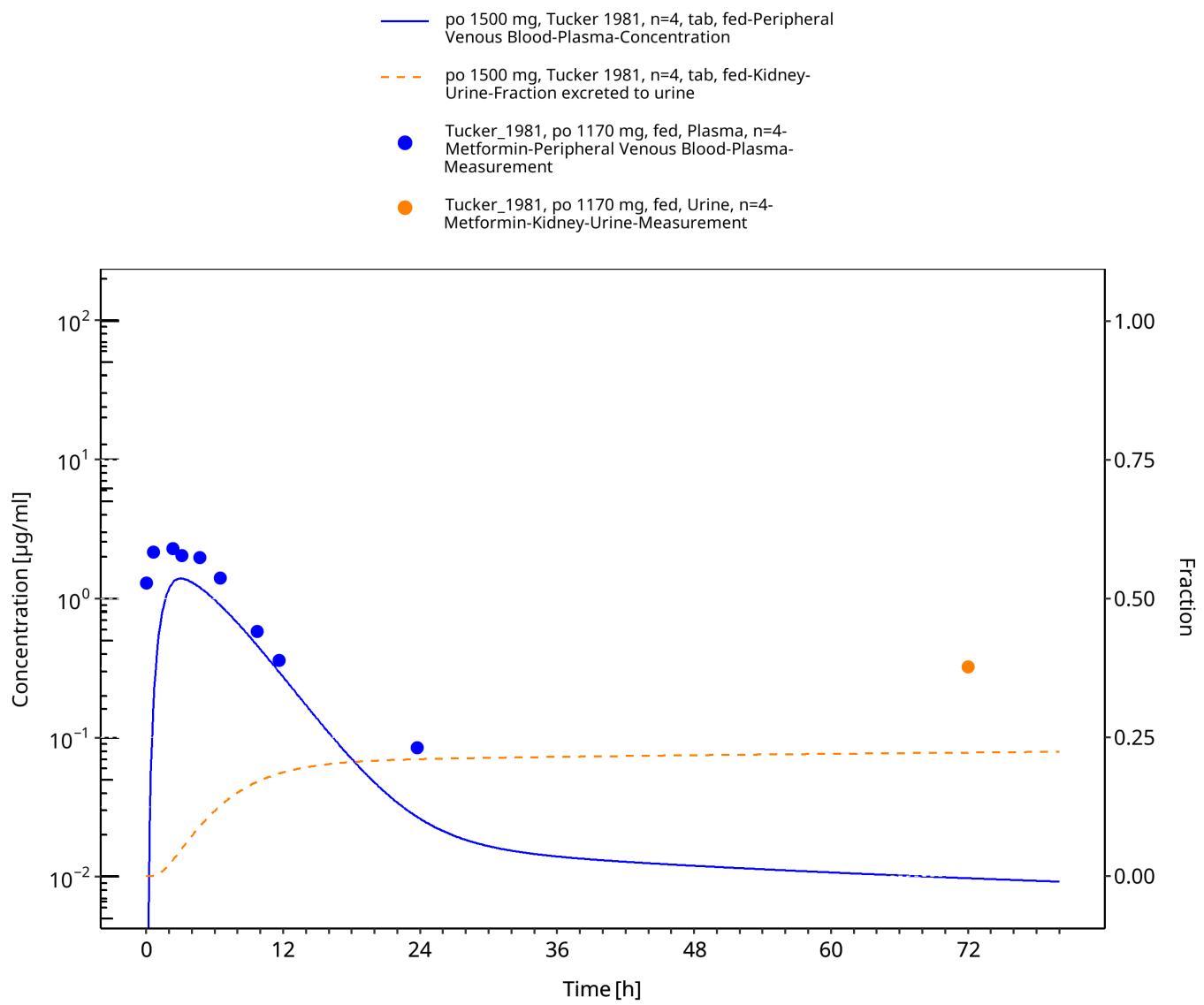


Figure 3-40: Metformin - po (tab) 1500 mg_Tucker 1981

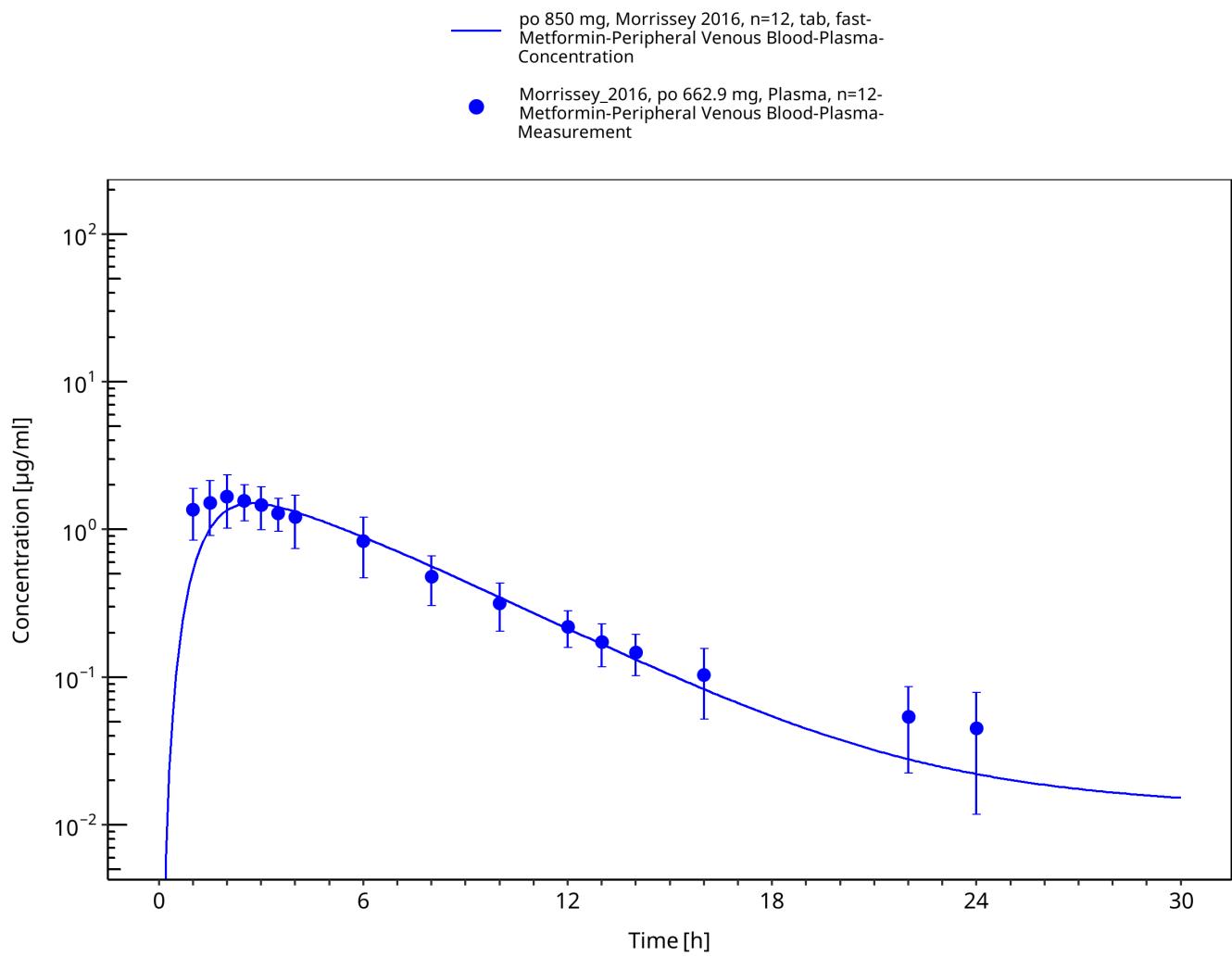


Figure 3-41: Metformin - po (tab) 850 mg_Morrissey 2016

4 Conclusion

The presented PBPK model adequately describes the intravenous and oral pharmacokinetics of metformin in adults.

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