

# Building and evaluation of a PBPK model for cimetidine in healthy adults

Version	2.0-OSP12.2
based on <i>Model Snapshot</i> and <i>Evaluation Plan</i>	<a href="https://github.com/Open-Systems-Pharmacology/Cimetidine-Model/releases/tag/v2.0">https://github.com/Open-Systems-Pharmacology/Cimetidine-Model/releases/tag/v2.0</a>
OSP Version	12.2
Qualification Framework Version	3.5

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

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

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# 1 Introduction

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Cimetidine is a histamine H<sub>2</sub> receptor antagonist that inhibits stomach acid production. It is mainly used as an antacid for the treatment of gastric and duodenal ulcers, Zollinger-Ellison syndrome and esophageal reflux.

The herein presented model was developed and published by Hanke et al. ([Hanke 2020](#)) and adjusted later on to PK-Sim V10 by refitting CYP3A4 K<sub>i</sub> and MATE1 K<sub>i</sub>.

Cimetidine is mainly excreted unchanged via the kidneys (40–80% of the dose) with a high renal clearance of 400 ml/min. Metabolism is reported to account for 25– 40% of the total elimination of cimetidine, with less than 2% of the dose excreted unchanged with the bile. Cimetidine inhibits several transporters and CYP enzymes and it is recommended by the FDA as strong inhibitor of OCT2/MATE and as weak inhibitor of CYP3A4 and CYP2D6 for the use in clinical DDI studies and drug labeling.

The cimetidine model was established using 27 clinical studies, covering a dosing range from 100 to 800 mg. The final model applies active uptake of cimetidine into the liver by OCT1, uptake into the kidney by OAT3 and secretion from the kidney into the urine by MATE1, as well as an unspecific hepatic clearance and passive renal glomerular filtration.

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

# 2 Methods

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## 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 ([Willmann 2007](#)). 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 ([PK-Sim Ontogeny Database Version 7.3](#)) or otherwise referenced for the specific process.

The final model applies active uptake of cimetidine into the liver by OCT1, uptake into the kidney by OAT3 and secretion from the kidney into the urine by MATE1, as well as an unspecific hepatic clearance and passive renal glomerular filtration. The transporters were integrated into the PBPK model using the ([PK-Sim Ontogeny Database Version 7.3](#)) and is described in detail in [Hanke 2020](#). For PK-Sim V10, CYP3A4  $K_i$  and MATE1  $K_i$  were adjusted to improve the performance in CYP3A4 and MATE1 interaction scenarios. For further details, see [Section 2.3](#).

First, a base PBPK model was built using clinical data including single and multiple dose studies with intravenous and oral applications of cimetidine to find an appropriate structure to describe the pharmacokinetics in plasma. This PBPK model was developed using a typical European individual adjusted to the demography of the respective study population.

Oral administration of cimetidine in the fasted state frequently produces two plasma concentrations peaks. These double peaks are probably caused by the phasic gastrointestinal motility that controls gastric emptying in the fasted state. To describe the very different shapes of the observed mean cimetidine plasma profiles, split dose administration protocols for all studies of cimetidine administered orally in the fasted state were optimized in a NONMEM analysis (see [Hanke 2020](#)). The resulting split dose administration protocols were then implemented and used for the PBPK modeling of the respective cimetidine studies.

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

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### 2.2.1 In vitro / physico-chemical Data

A literature search was performed to collect available information on physicochemical properties of cimetidine. The obtained information from literature is summarized in the table below.

Parameter	Unit	Value	Source	Description
MW	g/mol	252.34	Wishart 2006	Molecular weight
pK <sub>a</sub> 1		6.93 (base)	Avdeef 2001	Acid dissociation constant
pK <sub>a</sub> 2		13.38 (acid)	Wishart 2006	Acid dissociation constant
Solubility (pH)	mg/L	24.00 (6.8)	Avdeef 2001	Water solubility
logP		0.48	Avdeef 2001	Partition coefficient between octanol and water
f <sub>u</sub>	%	78.00	Taylor 1978	Fraction unbound in plasma
B/P ratio		0.98	Somogyi 1983	Blood to plasma ratio
OCT1 K <sub>m</sub>	μmol/l	2600	Umeshara 2007	Michaelis-Menten constant
OAT3 K <sub>m</sub>	μmol/l	149	Tahara 2005	Michaelis-Menten constant
MATE1 K <sub>m</sub>	μmol/l	8.0	Ohta 2005	Michaelis-Menten constant
OCT1 K <sub>i</sub>	μmol/l	104	Ito 2012	Inhibition constant for competitive inhibition
OCT2 K <sub>i</sub>	μmol/l	124	Ito 2012	Inhibition constant for competitive inhibition
MATE1 K <sub>i</sub> (refitted in PK-Sim V10)	μmol/l	3.8 (0.65)	Ito 2012	Inhibition constant for competitive inhibition
CYP3A4 K <sub>i</sub> (refitted in PK-Sim V10)	μmol/l	268 (30.51266)	Wrighton 1994	Inhibition constant for competitive inhibition

## 2.2.2 Clinical Data

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

### 2.2.2.1 Model Building

The following studies were used for model building:

Publication	Arm / Treatment / Information used for model building
Bodemar 1981	Peptic ulcer patients receiving a single intravenous dose of 200 mg and oral doses of 200, 400 and 800 mg
Morgan 1983	Peptic ulcer patients receiving a single intravenous dose of 200 mg (5 min infusion)
Bodemar 1979	Healthy subjects receiving single oral doses of 200 and 400mg (tablet)
Walkenstein 1978	Healthy subjects receiving a single oral dose of 300mg (solution)
D'Angio 1986	Healthy subjects receiving a single oral dose of 300mg (tablet)

### 2.2.2.2 Model verification

The following studies were used for model verification:

Publication	Arm / Treatment / Information used for model verification
Grahnen 1979	Healthy subjects receiving a single intravenous dose of 100 mg and a single oral dose of 400 mg (tablet)
Larsson 1982	Peptic ulcer patients receiving a single intravenous dose of 200 mg
Mihaly 1984	Peptic ulcer patients receiving a single intravenous and a single oral dose of 200 mg
Morgan 1983	Peptic ulcer patients receiving a single intravenous dose of 200 mg (30 min infusion)
Lebert 1981	Healthy subjects receiving a single intravenous dose of 300 mg (2 min infusion)
Walkenstein 1978	Healthy subjects receiving a single intravenous dose of 300 mg (2 min infusion) and a single oral dose of 300 mg (tablet)
Kanto 1981	Healthy subjects receiving a single oral dose of 200 mg
Burland 1975	Healthy subjects receiving single oral doses of 200 mg solution and capsule
Bodemar 1979	Peptic ulcer patients receiving a single oral dose of 200 mg (tablet)
Bodemar 1981	Peptic ulcer patients receiving single oral doses of 800 mg and multiple oral doses of 200 and 400 mg
Barbhaiya 1995	Healthy subjects receiving multiple oral doses of 300 mg (tablet)
Somogyi 1981	Healthy subjects receiving a single oral dose of 400 mg (tablet)
Tiseo 1998	Healthy subjects receiving multiple oral doses of 800 mg (tablet)

### 2.2.2.3 Model update due to PK-Sim V10 conversion

As a consequence of updating the cimetidine PBPK model to PK-Sim version 10, the CYP3A4  $K_i$  value needed to be readjusted. For this purpose, AUC ratios of the following clinical DDI studies were used to inform  $K_i$  in an additional parameter identification:

Publication	Interaction of cimetidine with:
Kienlen 1993	Alfentanil
Abernethy 1983	Alprazolam and triazolam
Elliott 1984	Midazolam
Fee 1987	Midazolam
Greenblatt 1986	Intravenous and oral midazolam
Martinez 1999	Midazolam
Salonen 1986	Midazolam
Pourbaix 1985	Triazolam. NOTE: The interaction of cimetidine with alprazolam of this publication was not used for parameterization due to very long simulation duration!
Cox 1986	Triazolam
Friedman 1988	Triazolam

Similarly, MATE1  $K_i$  value was adjusted to reproduce the observed inhibition effect on metformin PK (<https://github.com/Open-Systems-Pharmacology/Cimetidine-Metformin-DDI>).

## 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

Cimetidine is reported to be actively taken up into the liver by OCT1 ([Umeshara 2007](#)), into the kidney by OAT3 ([Tahara 2005](#)) and secreted from the kidney into the urine by MATE1 ([Ohta 2010](#)).

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 method by [Rodgers and Rowland](#) and cellular permeability calculation by [PK-Sim Standard](#).

A [Lipophilicity](#) of 1.66 was back-calculated from the blood-to-plasma ratio of 0.98 ([Somogyi 1983, Hanke 2020](#)).

### 2.3.3 Metabolism, Elimination and Inhibition

Cimetidine is mainly excreted unchanged via the kidneys. Additionally, 25 to 40 % is hepatically metabolized via an unknown pathway.

Cimetidine inhibits several enzymes such as CYP3A4 and CYP2D6 as well as transporters such as OCT2, OCT2 and MATE.

## 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 (see [Section 2.2](#)).

Specific intestinal permeability, unspecific hepatic clearance (CLhep) and Kcat values for OCT1, OAT3 and MATE1 were reestimated in PK-Sim Version 10, and, therefore, do not correspond to the original values published by [Hanke 2020](#). The result of the final parameter identification is shown in the table below:

Model Parameter	Optimized Value	Unit
Specific intestinal permeability	5.26E-06	cm/min
CLhep	0.12	1/min
kcat OCT1	14098.32	1/min
kcat OAT3	2522831.10	1/min
kcat MATE1	159.47	1/min

As a result of updating the cimetidine PBPK model to PK-Sim V10, the interaction parameter CYP3A4  $K_i$  was fitted in a second step to improve the performance in CYP3A4 interactions. In detail, CYP3A4  $K_i$  was adjusted such that the error of the simulated AUC ratios of cimetidine with several CYP3A4 substrates vs. corresponding observed AUC ratios of the clinical studies (see [Section 2.2.2.3](#)) was minimized.

Model Parameter	Optimized Value	Unit
CYP3A4 $K_i$	30.51266	$\mu\text{mol/l}$

# 3 Results and Discussion

The PBPK model for cimetidine was developed and evaluated using publicly 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.

### Compound: Cimetidine

#### Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	24 mg/ml	Publication-Avdeef 2001	Measurement	True
Reference pH	6.8	Publication-Avdeef 2001	Measurement	True
Lipophilicity	1.655 Log Units	Parameter Identification	Measurement	True
Fraction unbound (plasma, reference value)	0.78	Publication-Taylor 1978	Measurement	True
Specific intestinal permeability (transcellular)	5.2554004942E-06 cm/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2021-09-13 17:00	Fit	True
Is small molecule	Yes			
Molecular weight	252.34 g/mol	Database-Drugbank		
Plasma protein binding partner	Unknown			

#### Calculation methods

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

#### Processes

## Systemic Process: Total Hepatic Clearance-Somogyi 1983

Species: Human

### Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.78	
Lipophilicity (experiment)	1.655 Log Units	
Plasma clearance	0 ml/min/kg	
Specific clearance	0.1209722937 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2021-09-13 17:00

## Transport Protein: MATE1-Paper

Molecule: MATE1

### Parameters

Name	Value	Value Origin
Transporter concentration	1 $\mu\text{mol/l}$	
Vmax	0 $\mu\text{mol/l/min}$	
Km	8 $\mu\text{mol/l}$	Parameter Identification
kcat	159.4749627996 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2021-09-13 17:00

## Transport Protein: OAT3-Paper

Molecule: OAT3

### Parameters

Name	Value	Value Origin
Transporter concentration	1 $\mu\text{mol/l}$	
Vmax	0 $\mu\text{mol/l/min}$	
Km	149 $\mu\text{mol/l}$	Publication-Tahara 2005
kcat	2522831.1016 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2021-09-13 17:00

## Transport Protein: OCT1-Paper

Molecule: OCT1

### Parameters

Name	Value	Value Origin
Transporter concentration	1 $\mu\text{mol/l}$	
Vmax	0 $\mu\text{mol/l/min}$	
Km	2600 $\mu\text{mol/l}$	Publication-Umehara 2007
kcat	14098.3224931732 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2021-09-13 17:00

## Systemic Process: Glomerular Filtration-GFR

Species: Human

### Parameters

Name	Value	Value Origin
GFR fraction	1	

## Inhibition: OCT1-Ito 2012

Molecule: OCT1

### Parameters

Name	Value	Value Origin
Ki	104 $\mu\text{mol/l}$	Publication-Ito 2012

## Inhibition: OCT2-Ito 2012

Molecule: OCT2

### Parameters

Name	Value	Value Origin
Ki	124 $\mu\text{mol/l}$	Publication-Ito 2012

## Inhibition: MATE1-Ito 2012

Molecule: MATE1

## Parameters

Name	Value	Value Origin
Ki	0.65 µmol/l	Parameter Identification-Parameter Identification- <a href="https://github.com/Open-Systems-Pharmacology/Cimetidine-Metformin-DDI">https://github.com/Open-Systems-Pharmacology/Cimetidine-Metformin-DDI</a>

## Inhibition: CYP3A4-Wrighton 1994

Molecule: CYP3A4

## Parameters

Name	Value	Value Origin
Ki	30.51266 µmol/l	Parameter Identification-Parameter Identification-Value adjusted in parameter identification outside of PK-Sim on 2023-11-14

## Formulation: Tablet

Type: Weibull

## Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	1 min	
Lag time	0 h	
Dissolution shape	10	
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 simulated versus observed plasma concentration, the second weighted residuals versus time.

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

<b>Group</b>	<b>GMFE</b>
iv administration	1.36
multiple oral administration	1.50
single oral administration	1.51
All	1.47

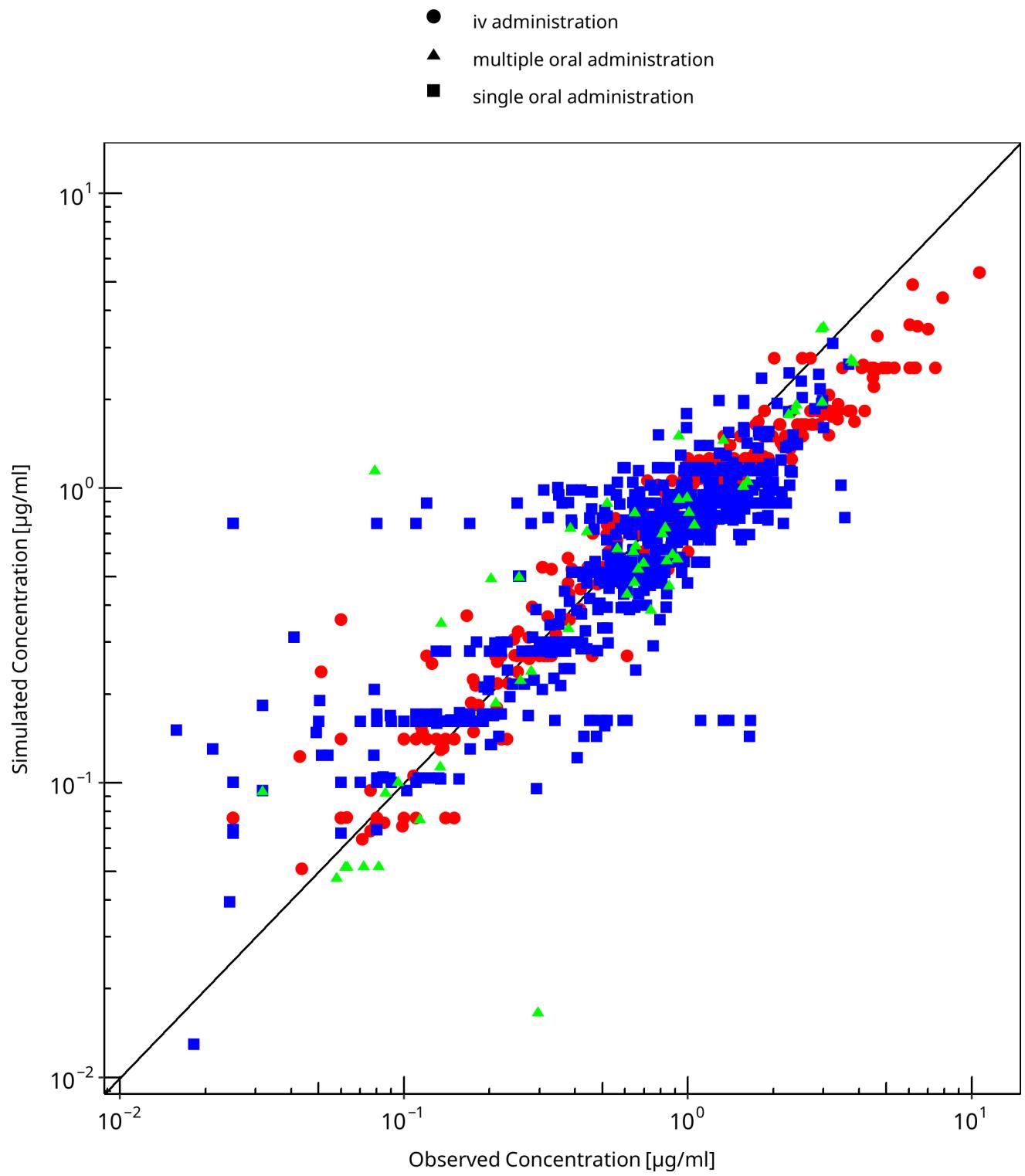
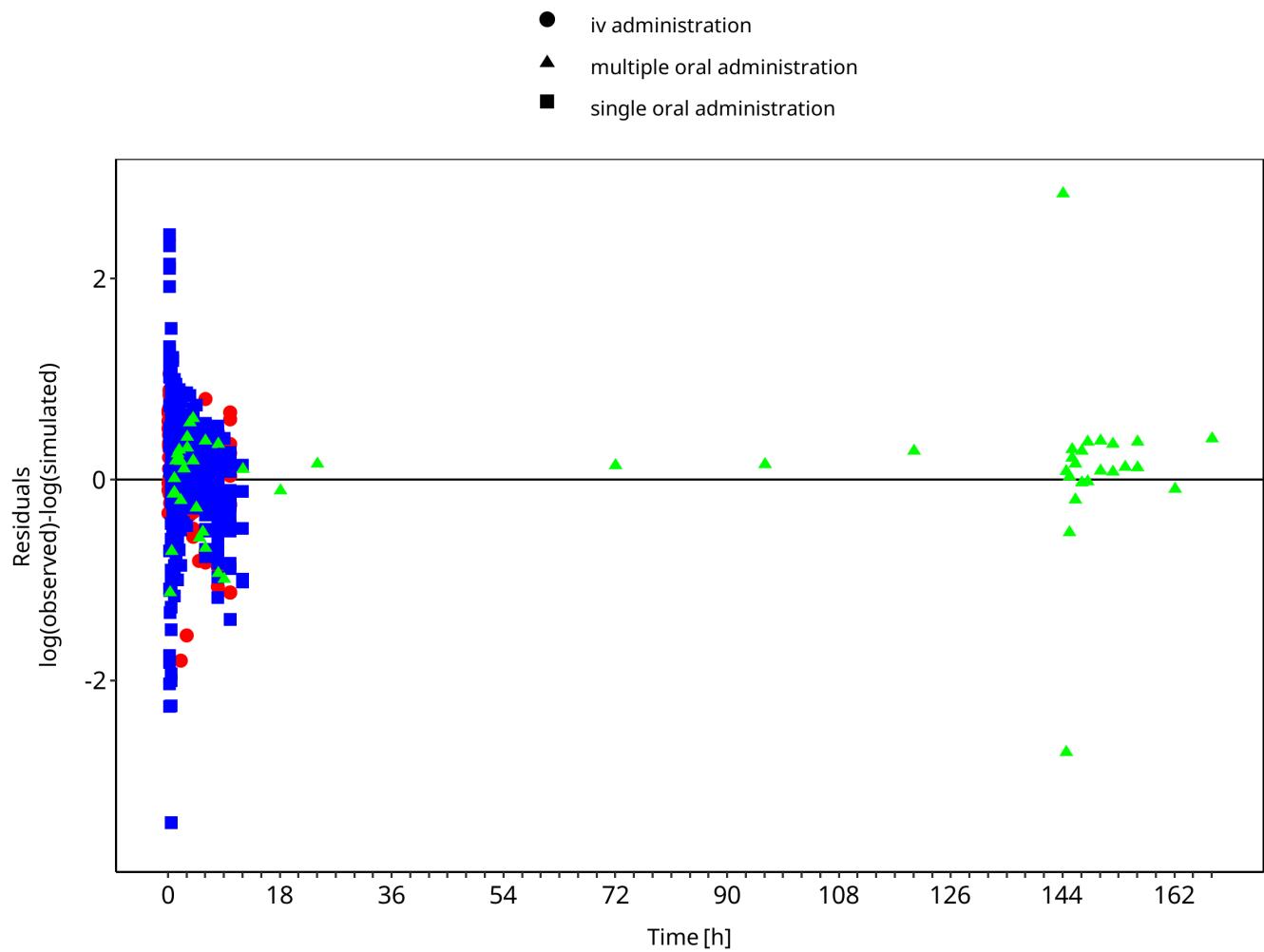


Figure 3-1: Goodness of fit plot for concentration in plasma



**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

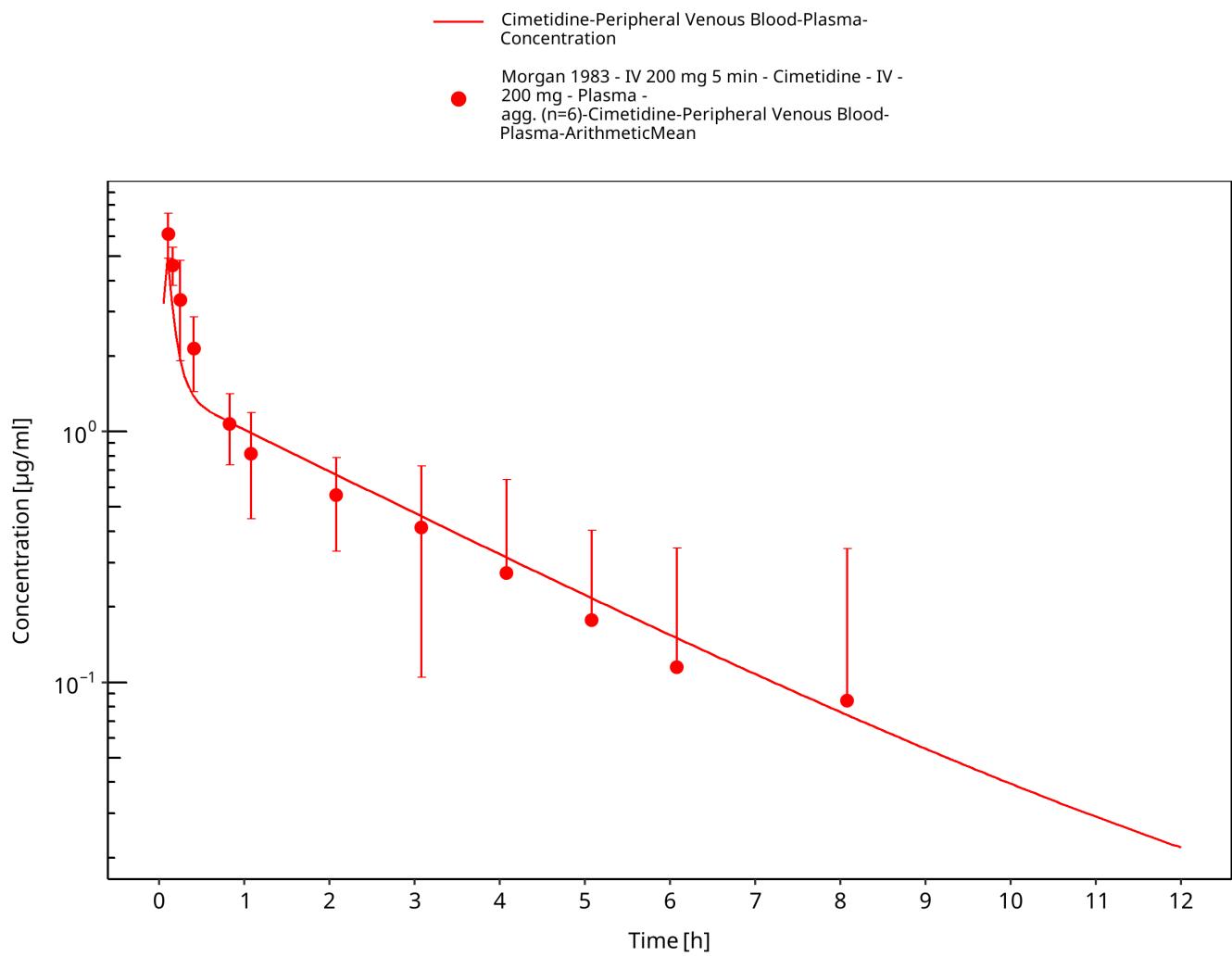


Figure 3-3: iv 200 mg (5 min),Morgan 1983, n=6

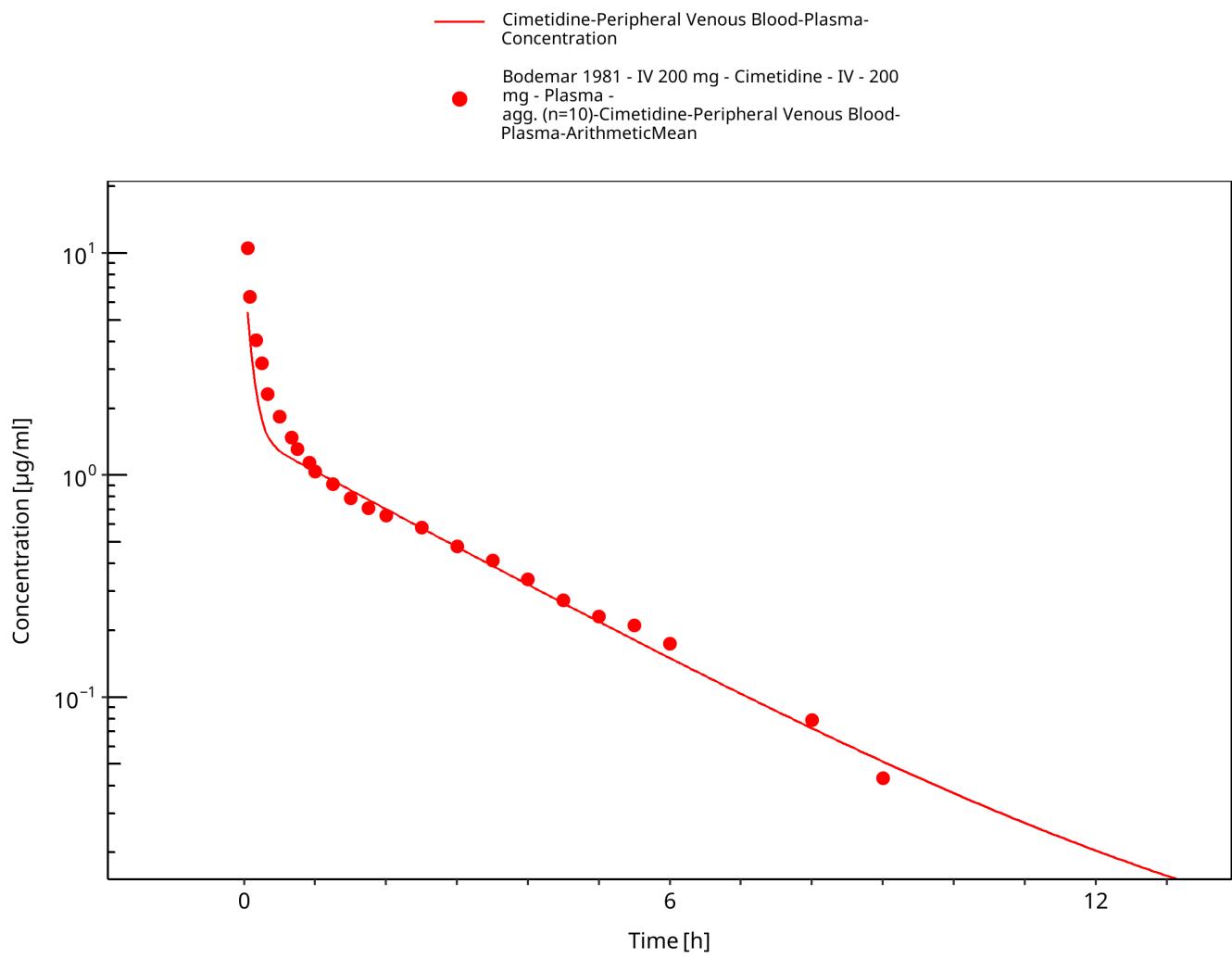


Figure 3-4: iv 200 mg, Bodemar 1981, n=10

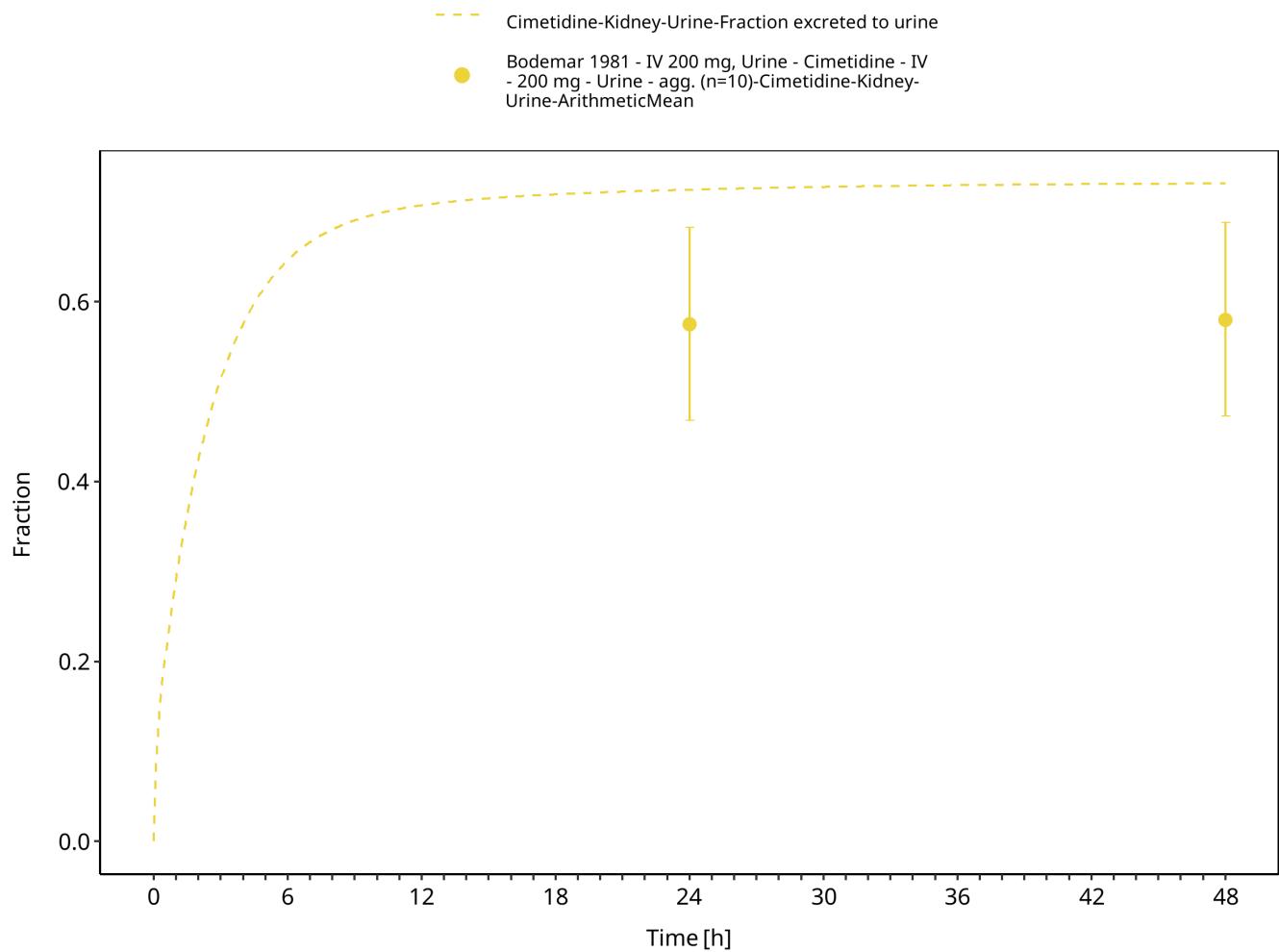


Figure 3-5: iv 200 mg, Bodemar 1981, n=10, urine

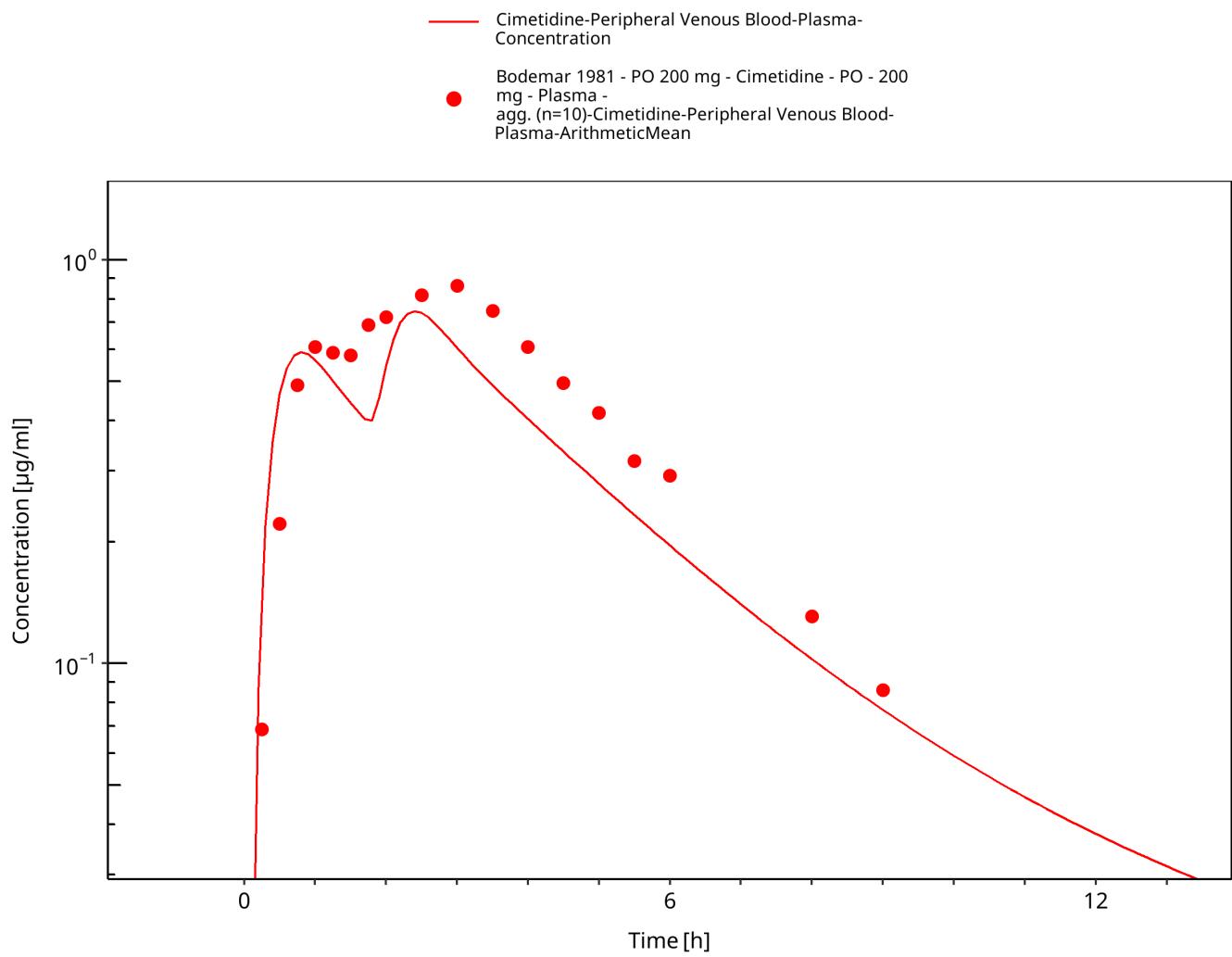


Figure 3-6: po 200 mg, Bodemar 1981, n=10

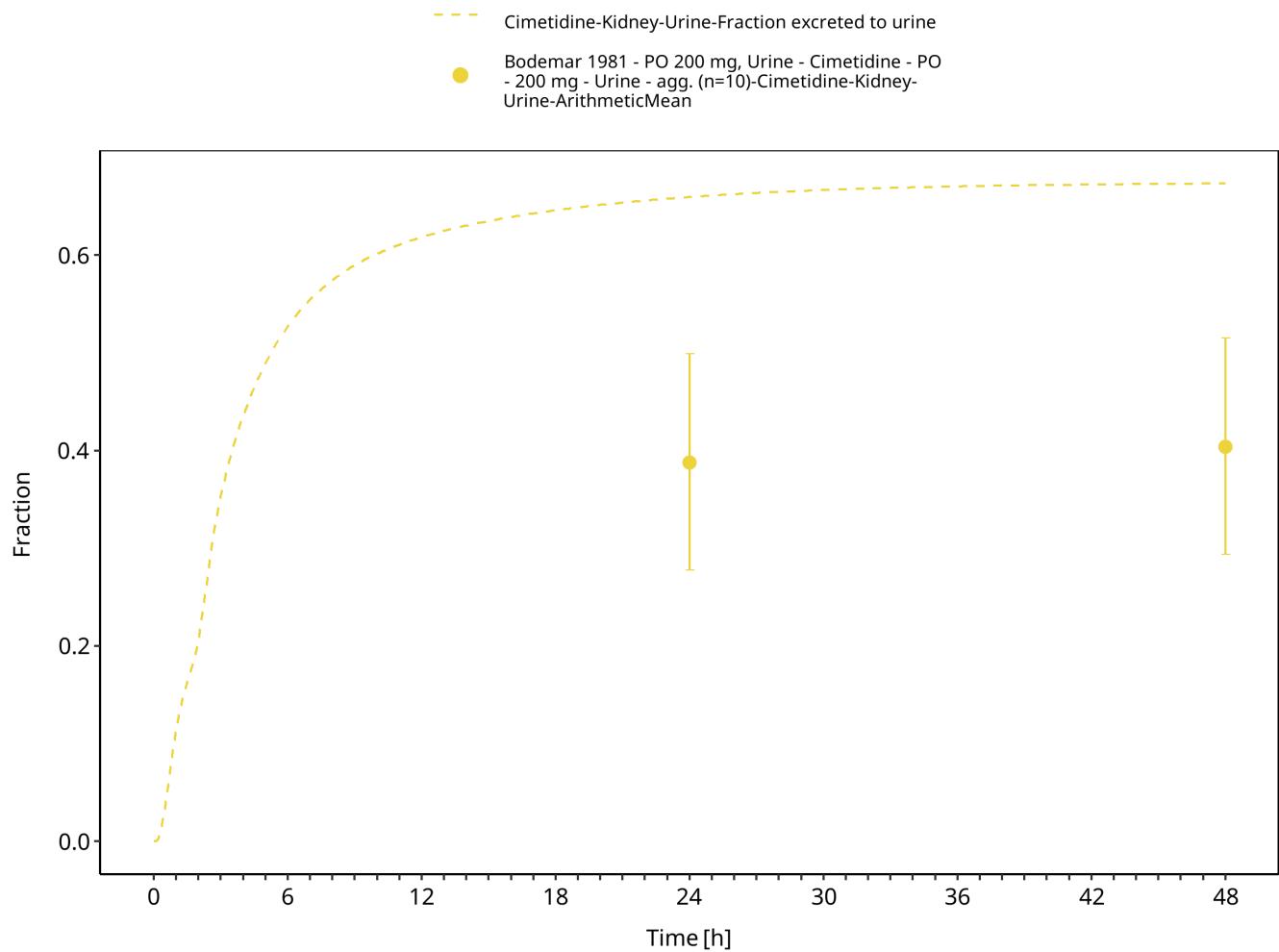
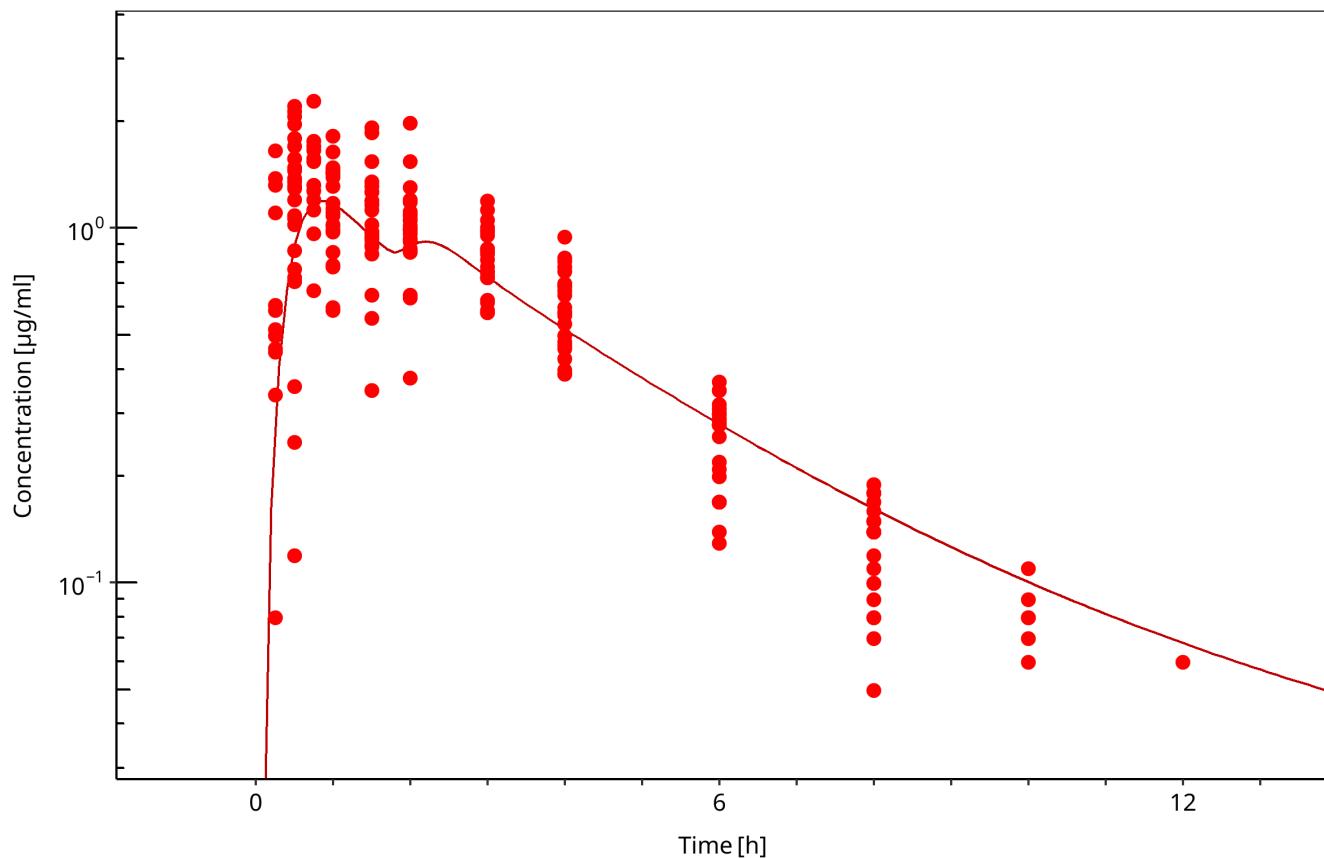


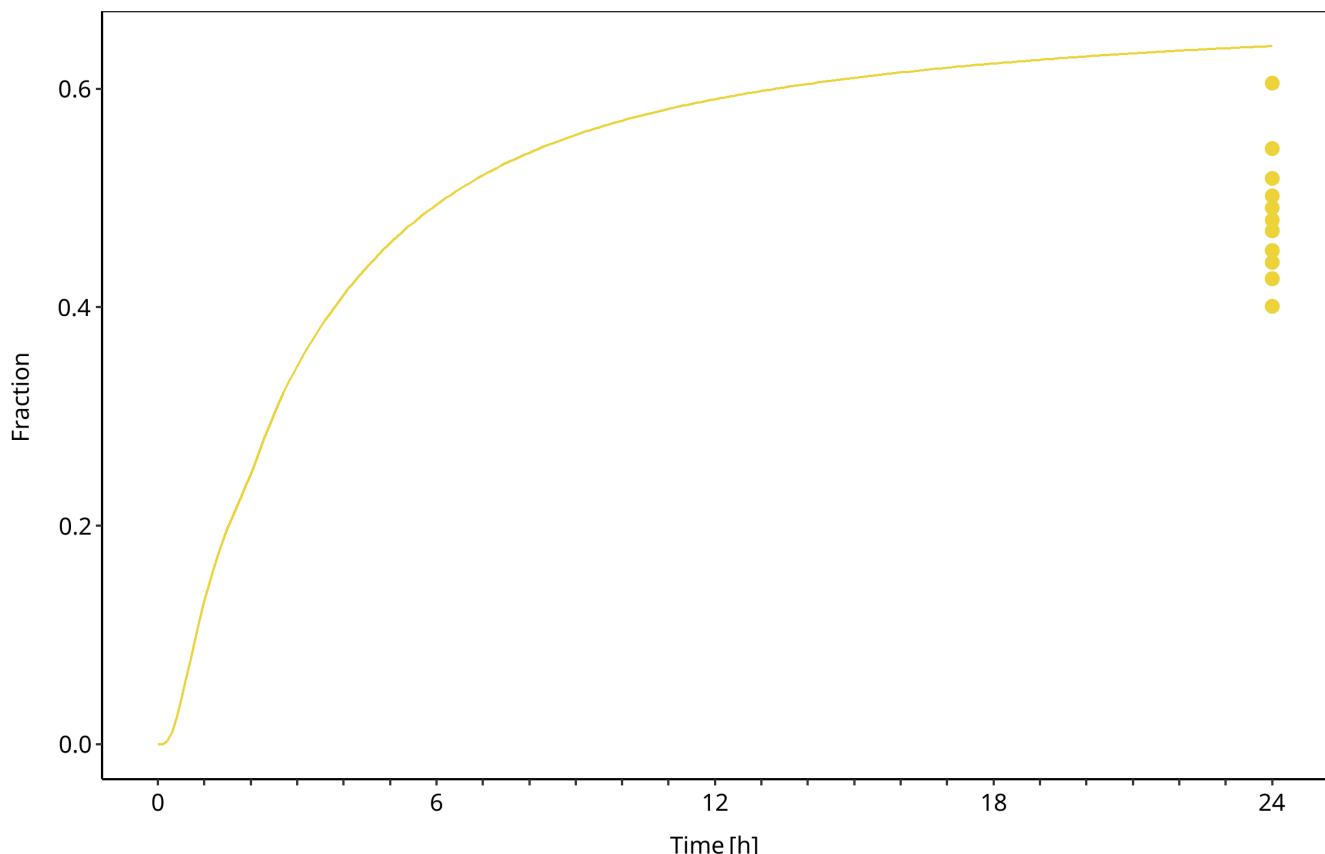
Figure 3-7: po 200 mg, Bodemar 1981, n=10, urine

- Cimetidine-Peripheral Venous Blood-Whole Blood-Concentration
- Walkenstein 1978 - PO 300 mg sol Subject 1 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 10 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 11 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 12 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 13 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 14 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 15 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 16 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 17 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 18 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 19 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 2 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 20 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 21 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 22 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 23 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 24 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 3 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 4 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 5 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 6 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 7 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 8 - Cimetidine - PO - 300 mg - Whole Blood - indiv.
  - Walkenstein 1978 - PO 300 mg sol Subject 9 - Cimetidine - PO - 300 mg - Whole Blood - indiv.

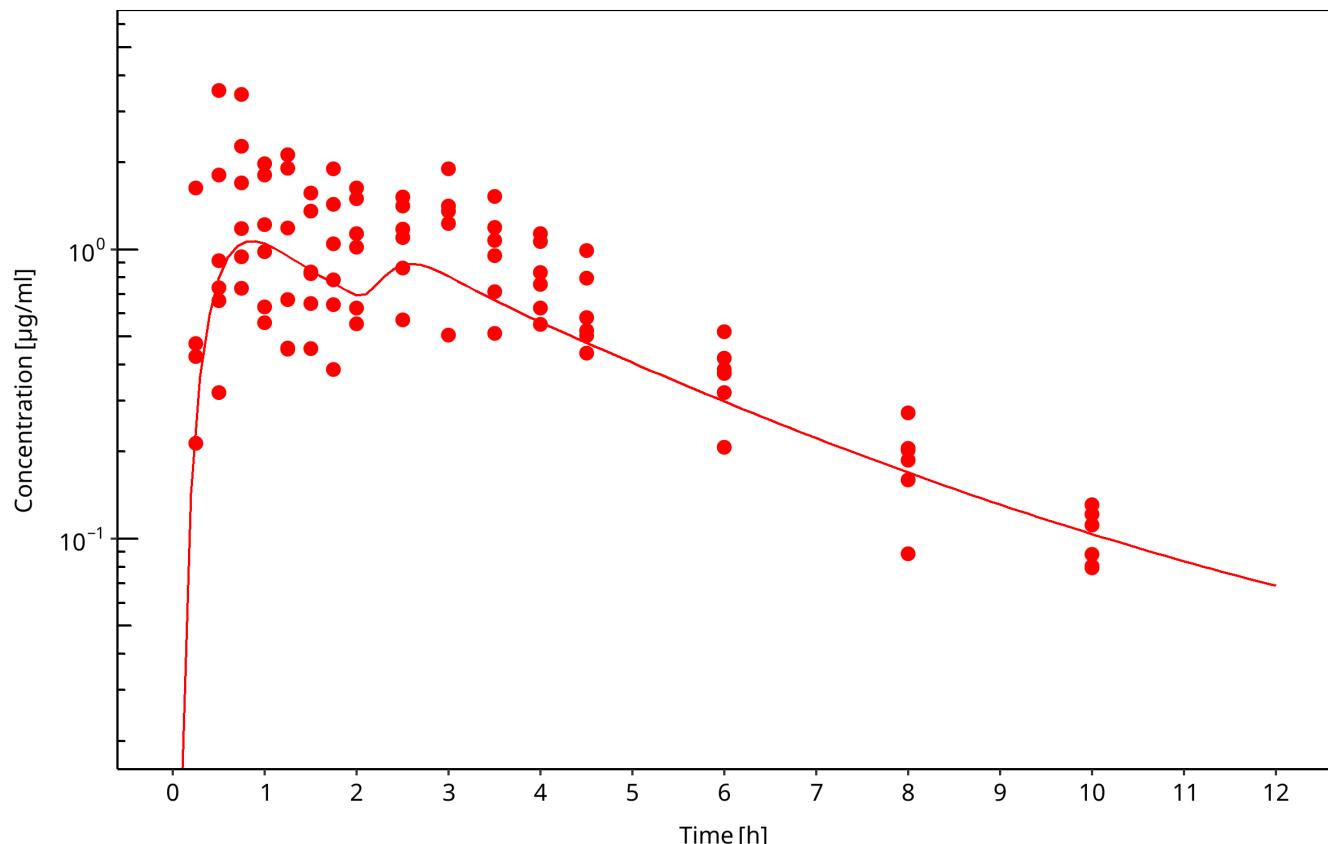
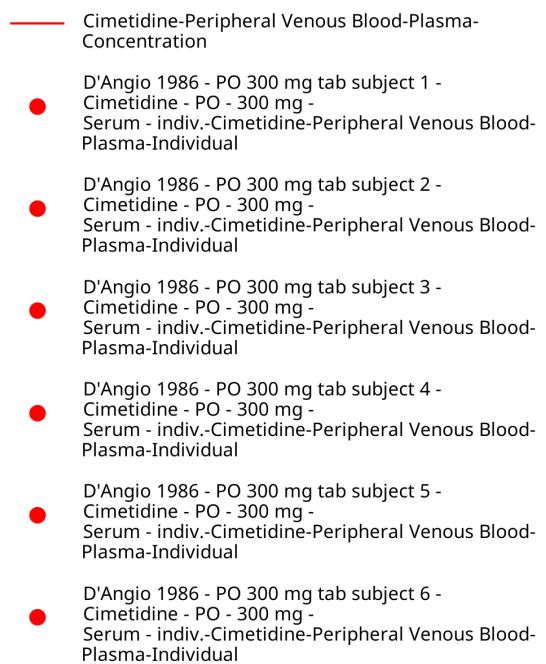


**Figure 3-8: po 300 mg (sol), Walkenstein 1978, n=24**

- Cimetidine-Kidney-Urine-Fraction excreted to urine
- Walkenstein 1978 - PO 300 mg urine Subject 1  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 10  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 11  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 12  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 2  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 3  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 4  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 5  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 6  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 7  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 8  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual
  - Walkenstein 1978 - PO 300 mg urine Subject 9  
- Cimetidine - PO - 300 mg - Urine - indiv.-  
Cimetidine-Kidney-Urine-Individual



**Figure 3-9: po 300 mg (sol), Walkenstein 1978, n=24, urine**



**Figure 3-10: po 300 mg (tab), D'Angio 1986, n=6**

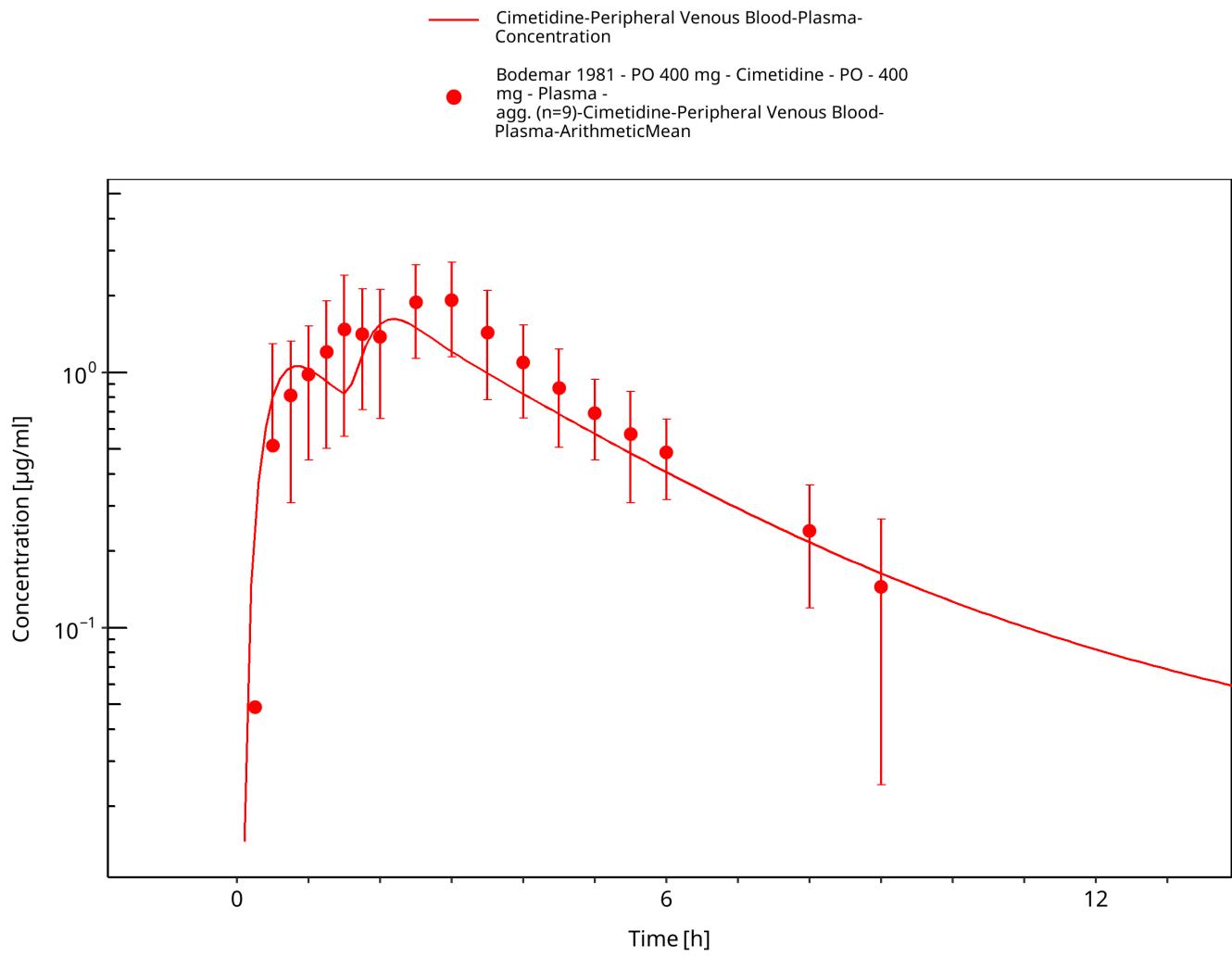


Figure 3-11: po 400 mg, Bodemar 1981, n=9

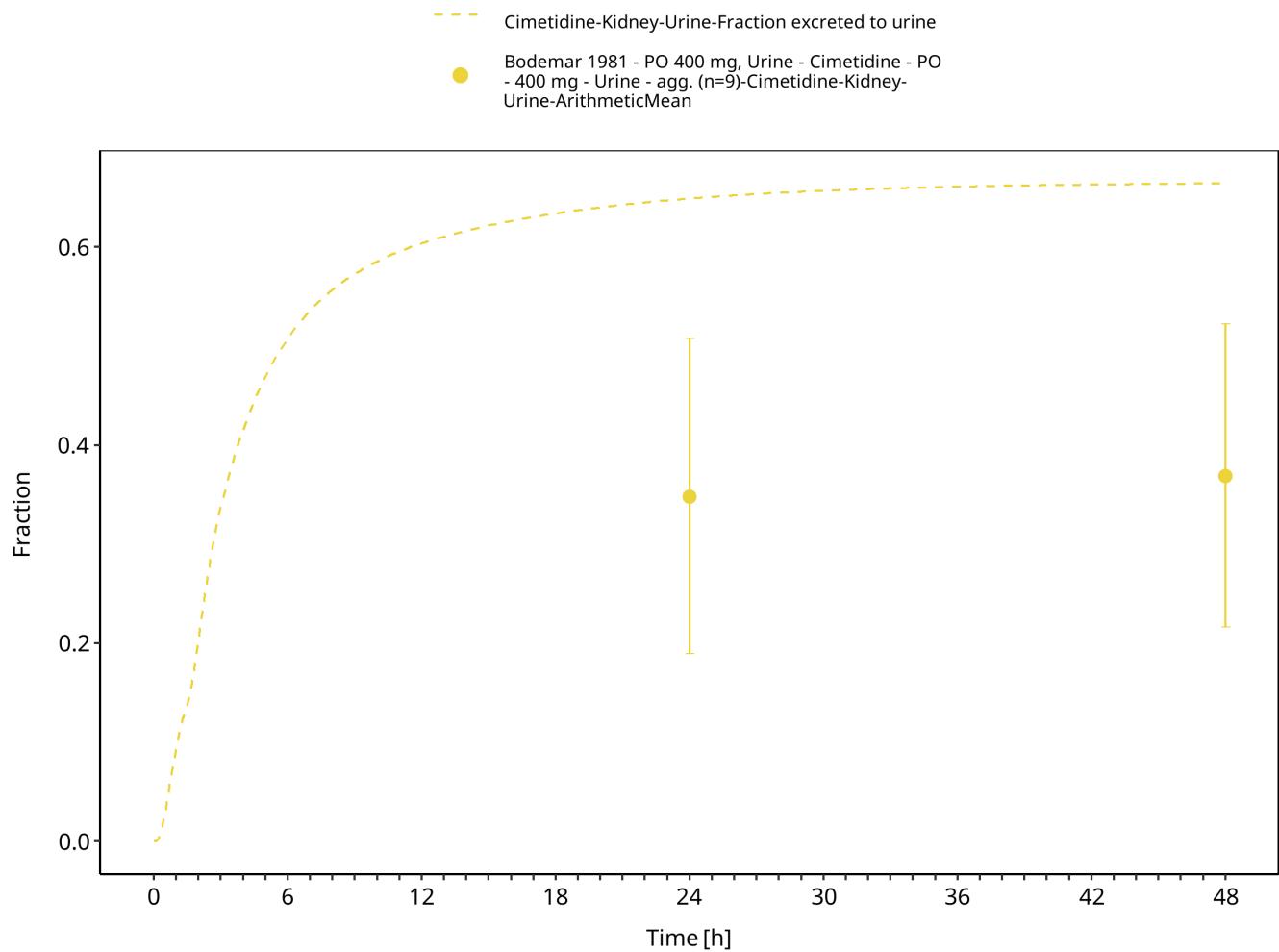


Figure 3-12: po 400 mg, Bodemar 1981, n=9, urine

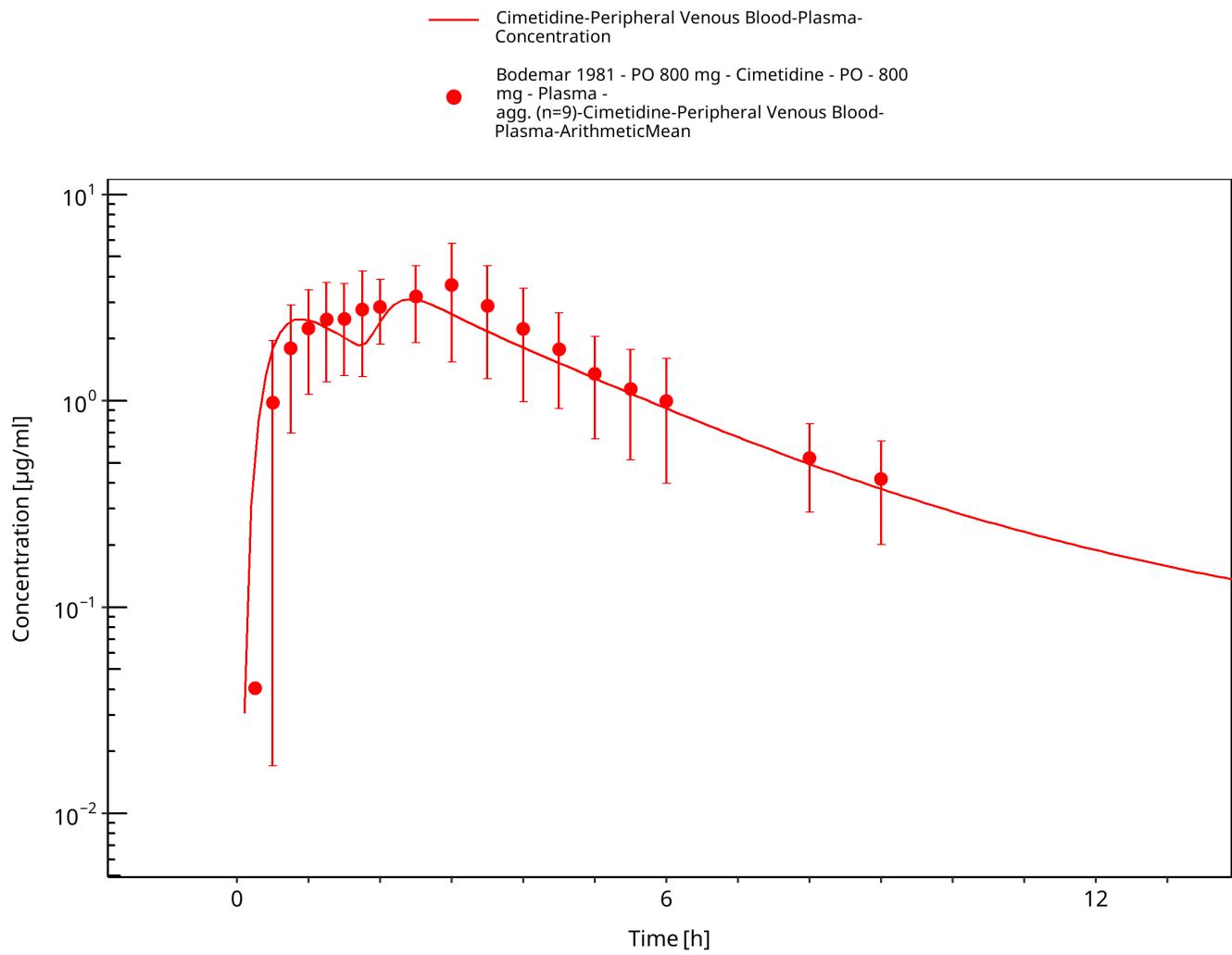


Figure 3-13: po 800 mg, Bodemar 1981, n=9

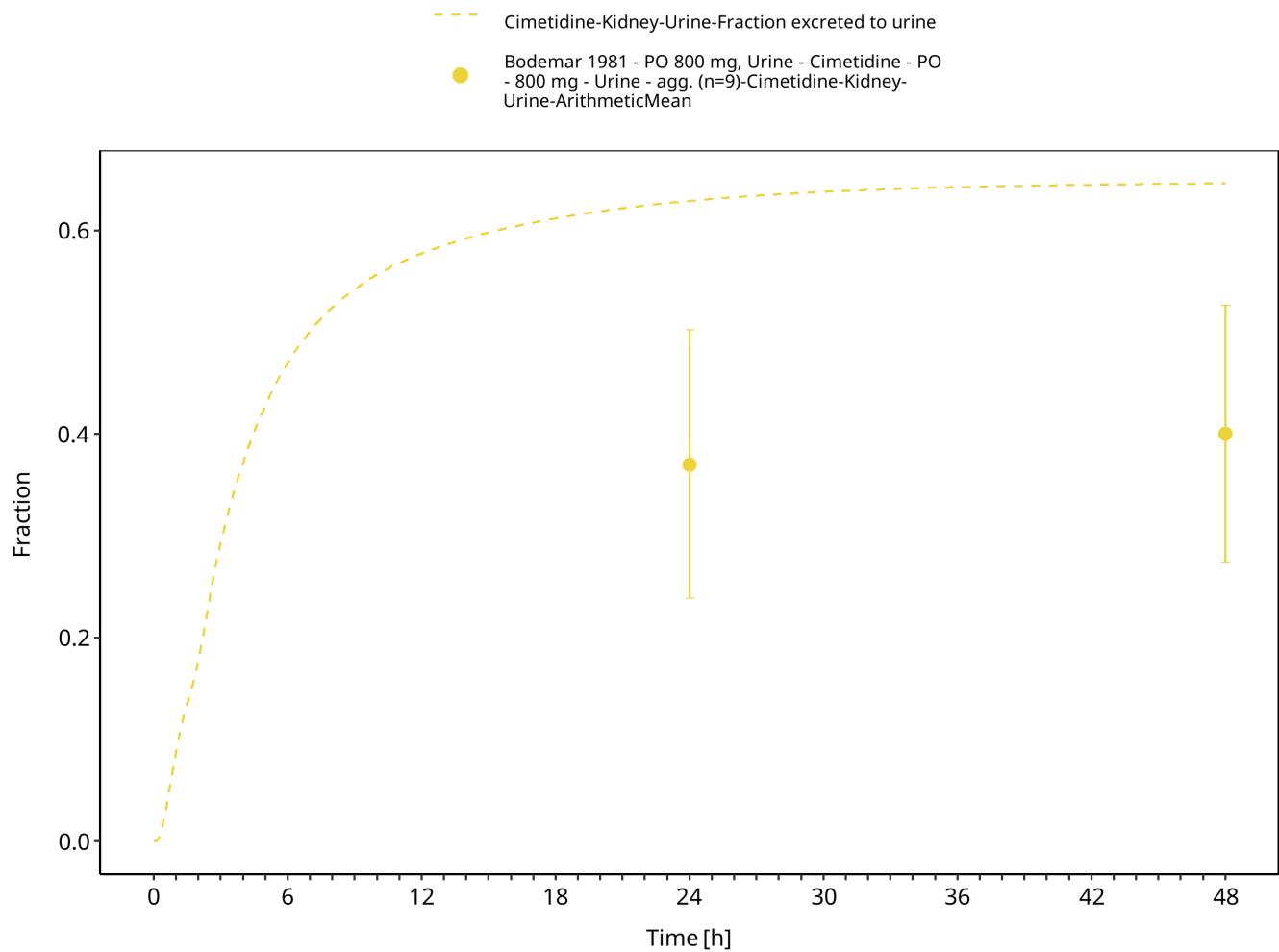


Figure 3-14: po 800 mg, Bodemar 1981, n=9, urine

### 3.3.2 Model Validation

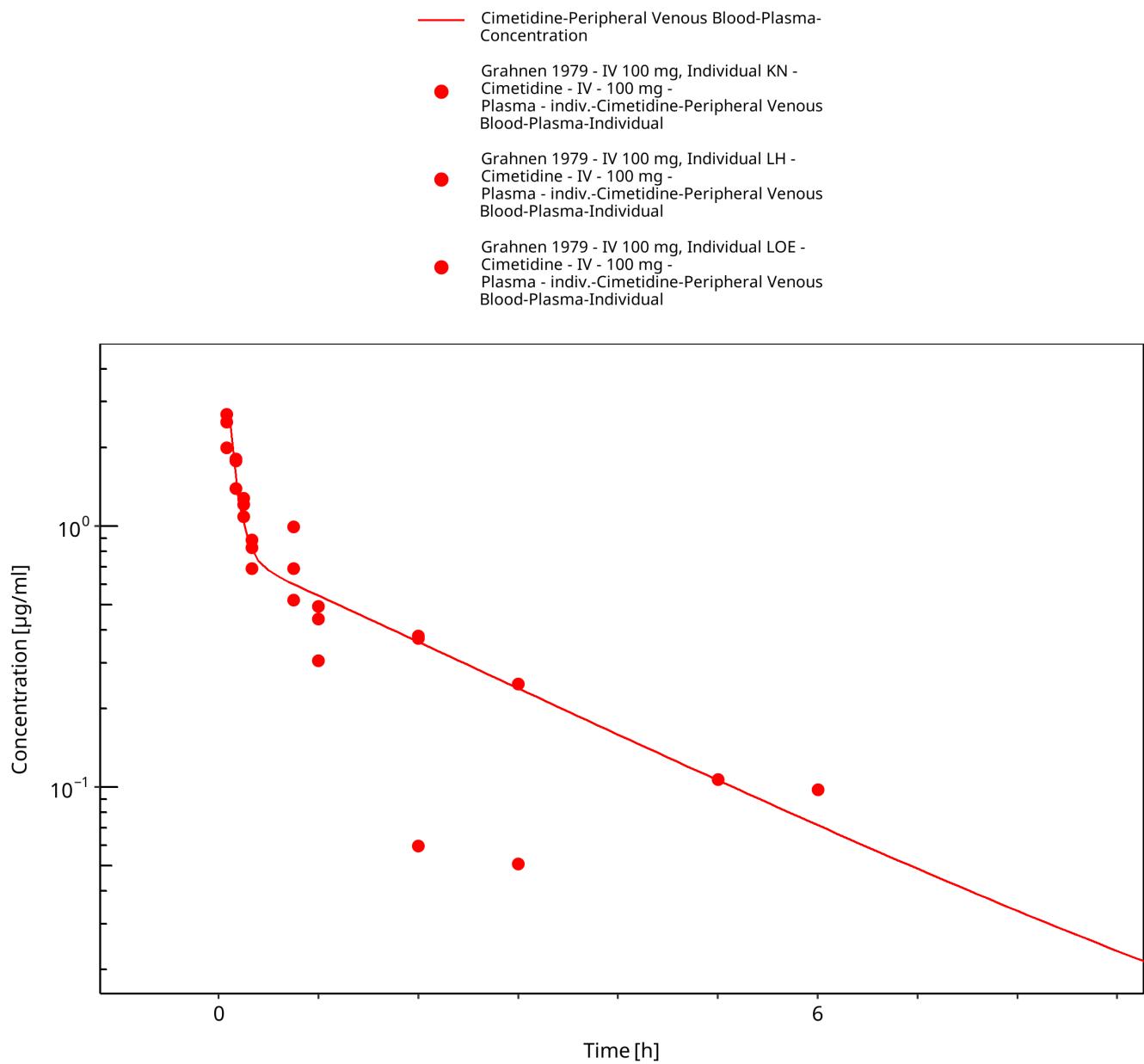
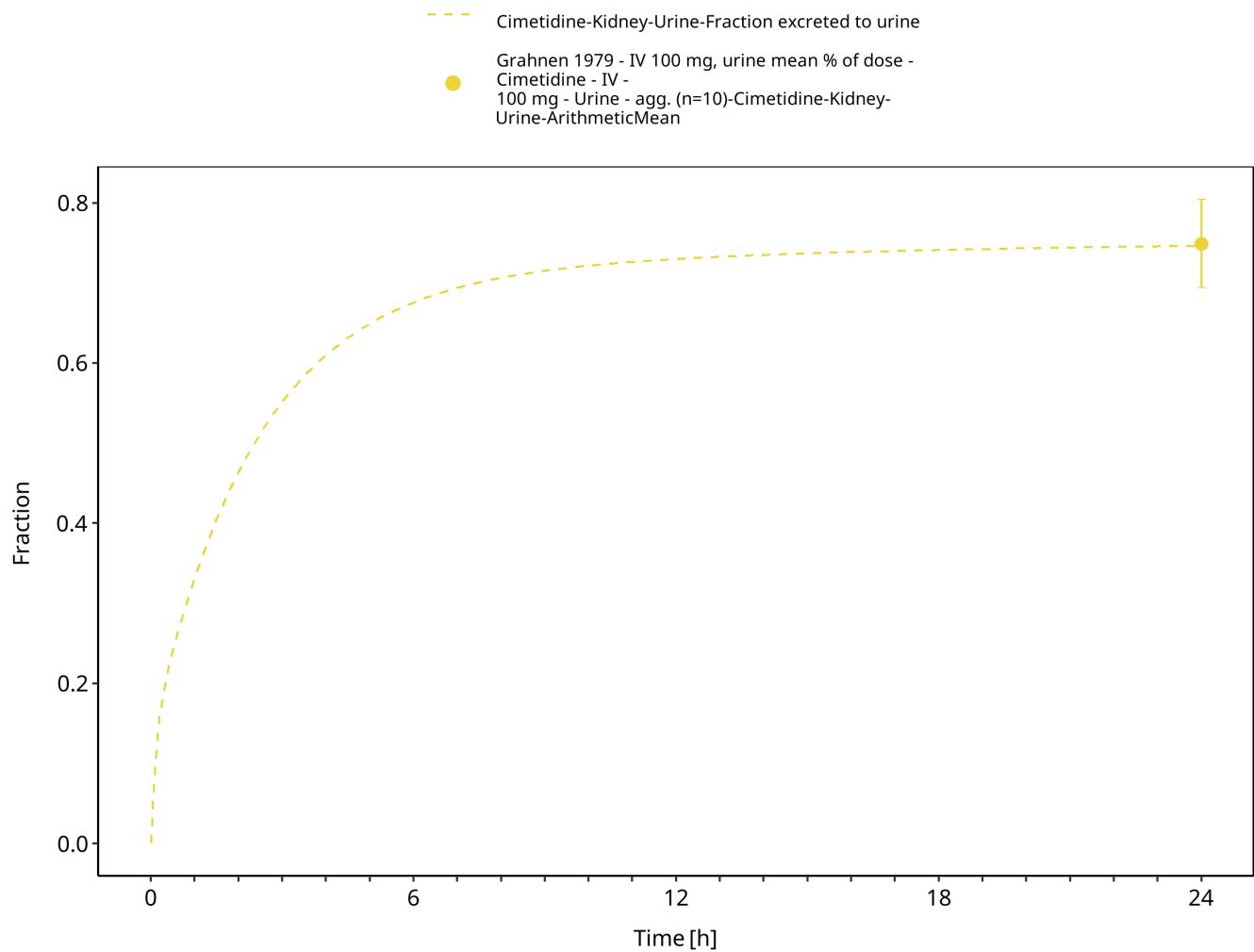


Figure 3-15: iv 100 mg (5 min), Grahnen 1979, n=3



**Figure 3-16: iv 100 mg (5 min), Grahnen 1979, n=3, urine**

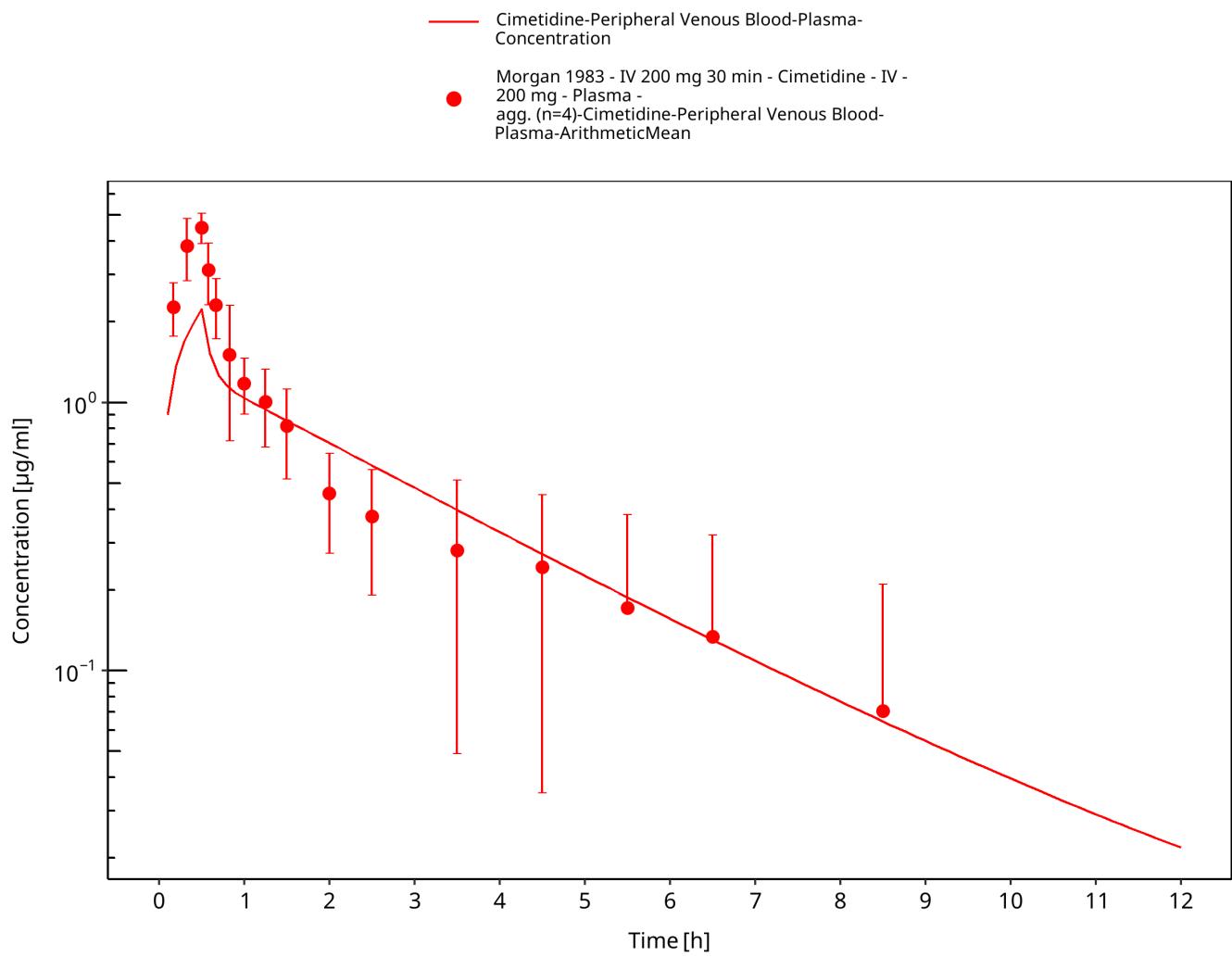


Figure 3-17: iv 200 mg (30 min),Morgan 1983, n=4

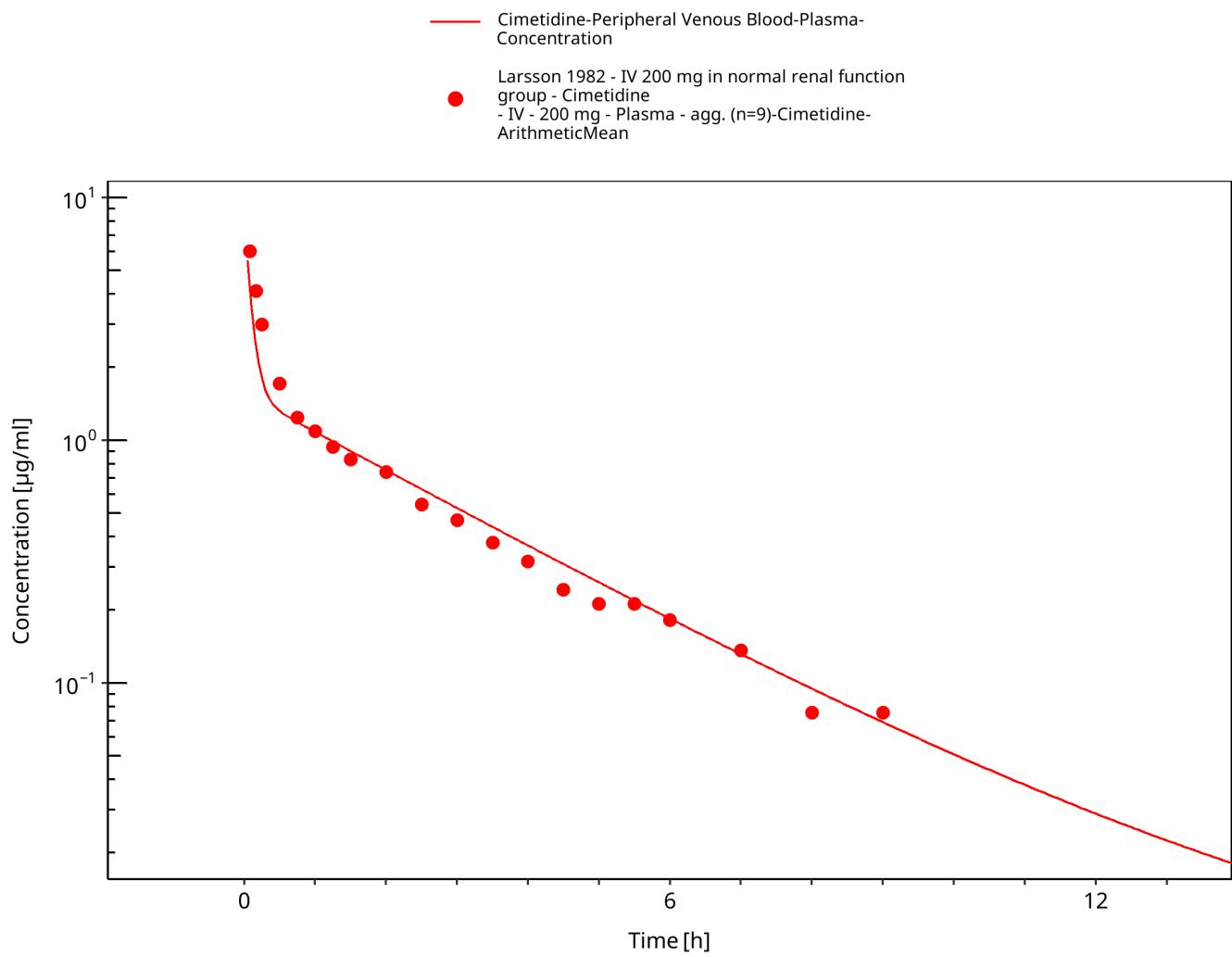
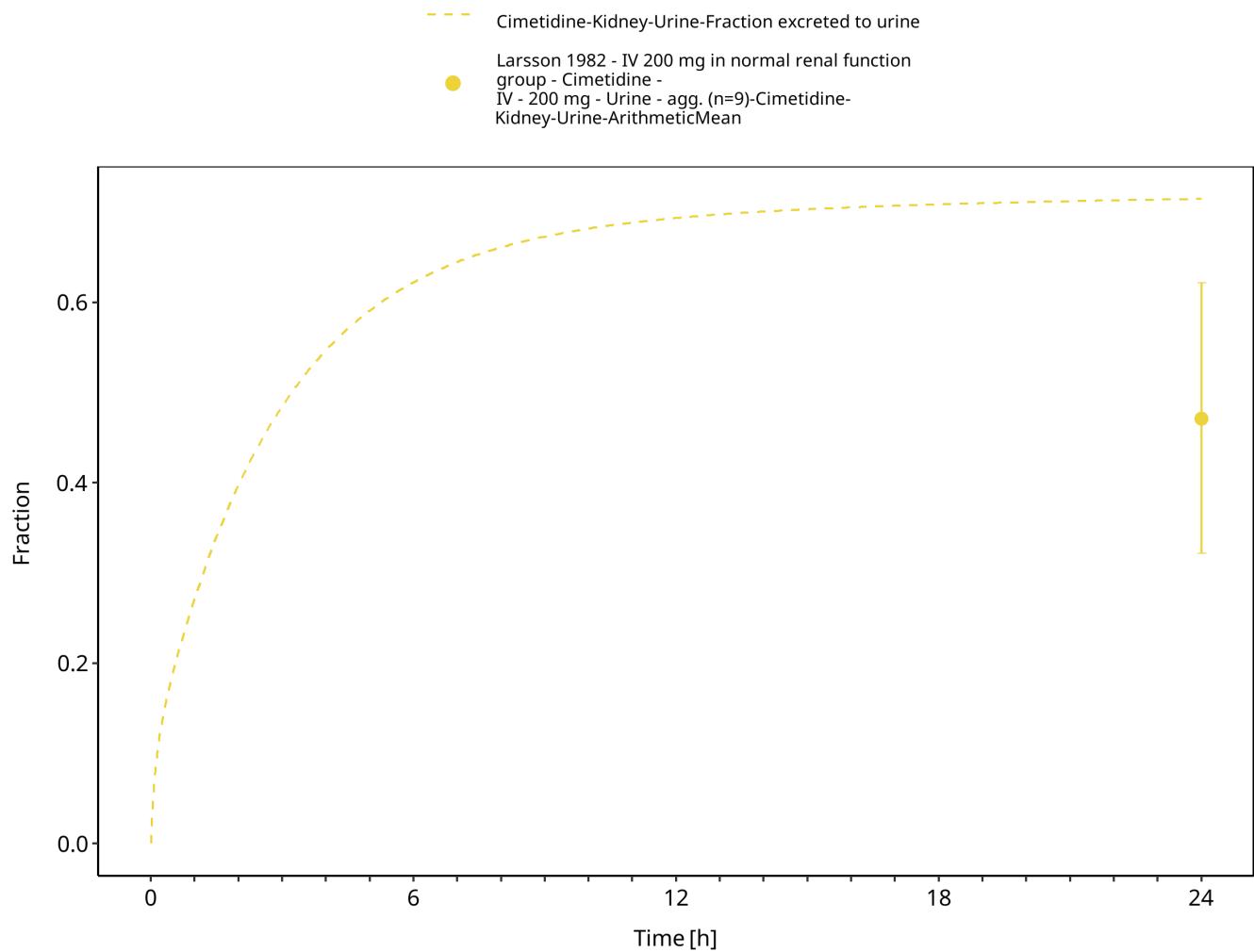


Figure 3-18: iv 200 mg, Larsson 1982, n=9



**Figure 3-19: iv 200 mg, Larsson 1982, n=9, urine**

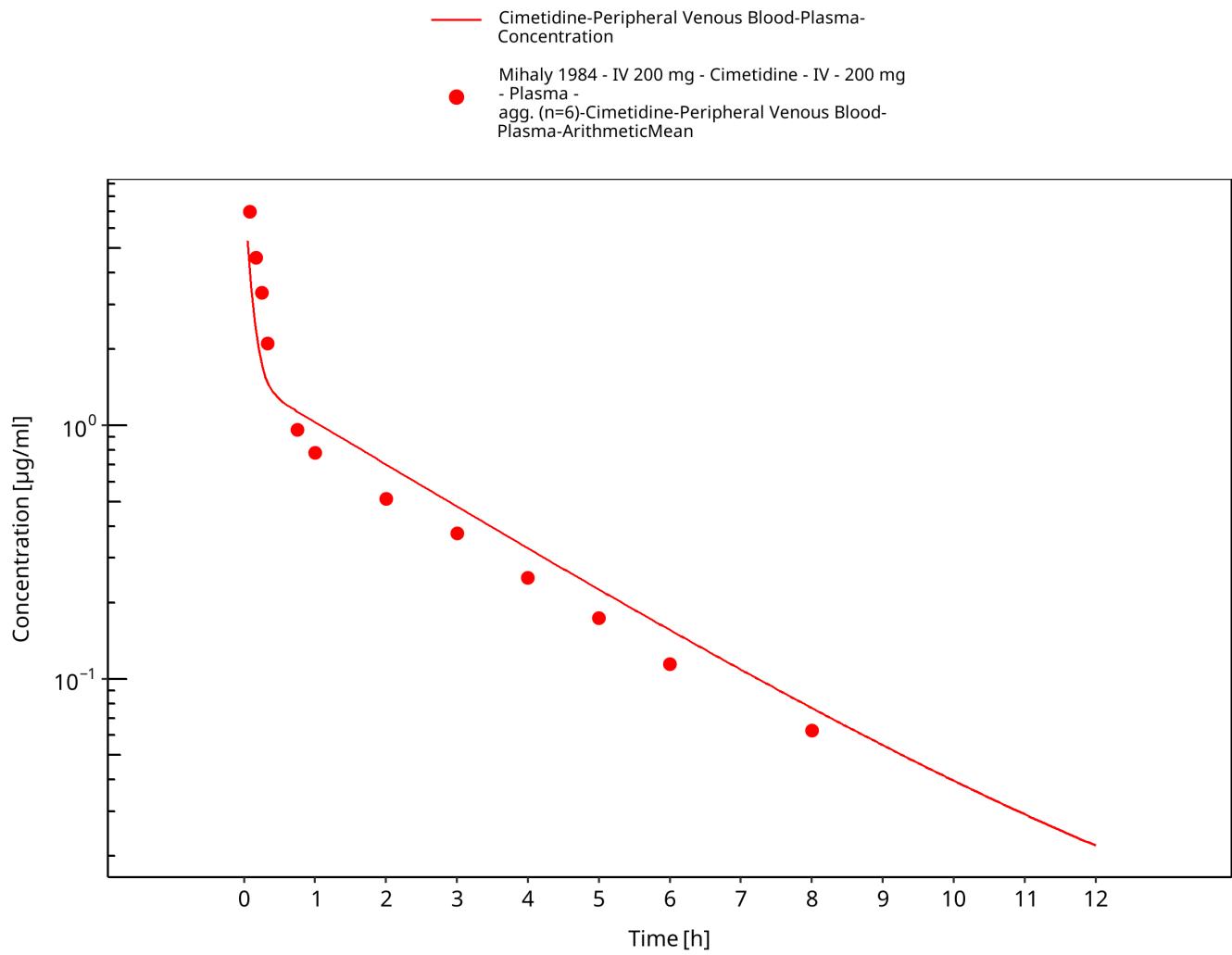


Figure 3-20: iv 200 mg, Mihaly 1984, n=6

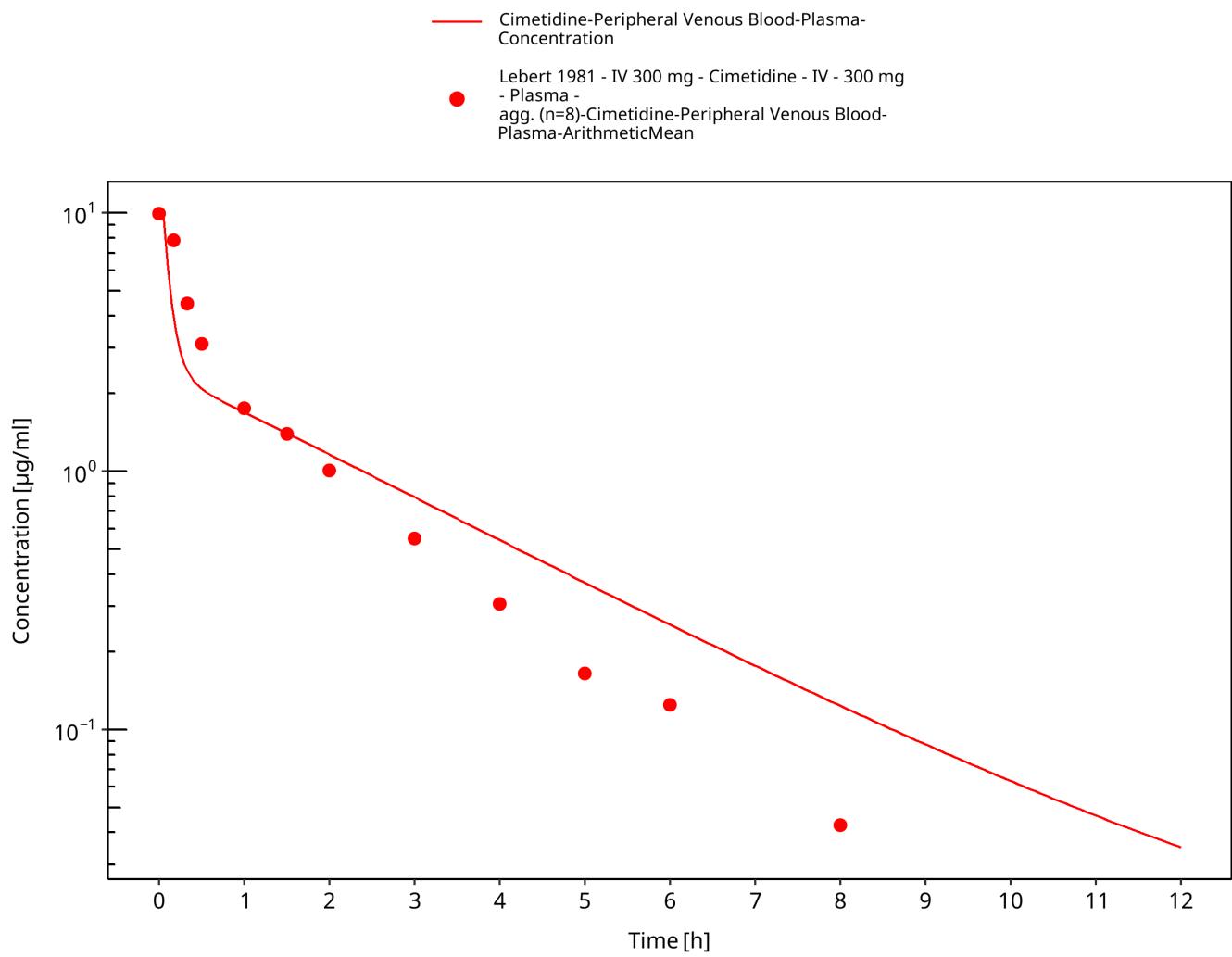


Figure 3-21: iv 300 mg (2 min), Lebert 1981, n=1

— Cimetidine-Peripheral Venous Blood-Whole Blood-Concentration

- Walkenstein 1978 - IV 300 mg Subject 1 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 10 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 11 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 12 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 2 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 3 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 4 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 5 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 6 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 7 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 8 - Cimetidine - IV - 300 mg - Whole Blood - indiv.
- Walkenstein 1978 - IV 300 mg Subject 9 - Cimetidine - IV - 300 mg - Whole Blood - indiv.

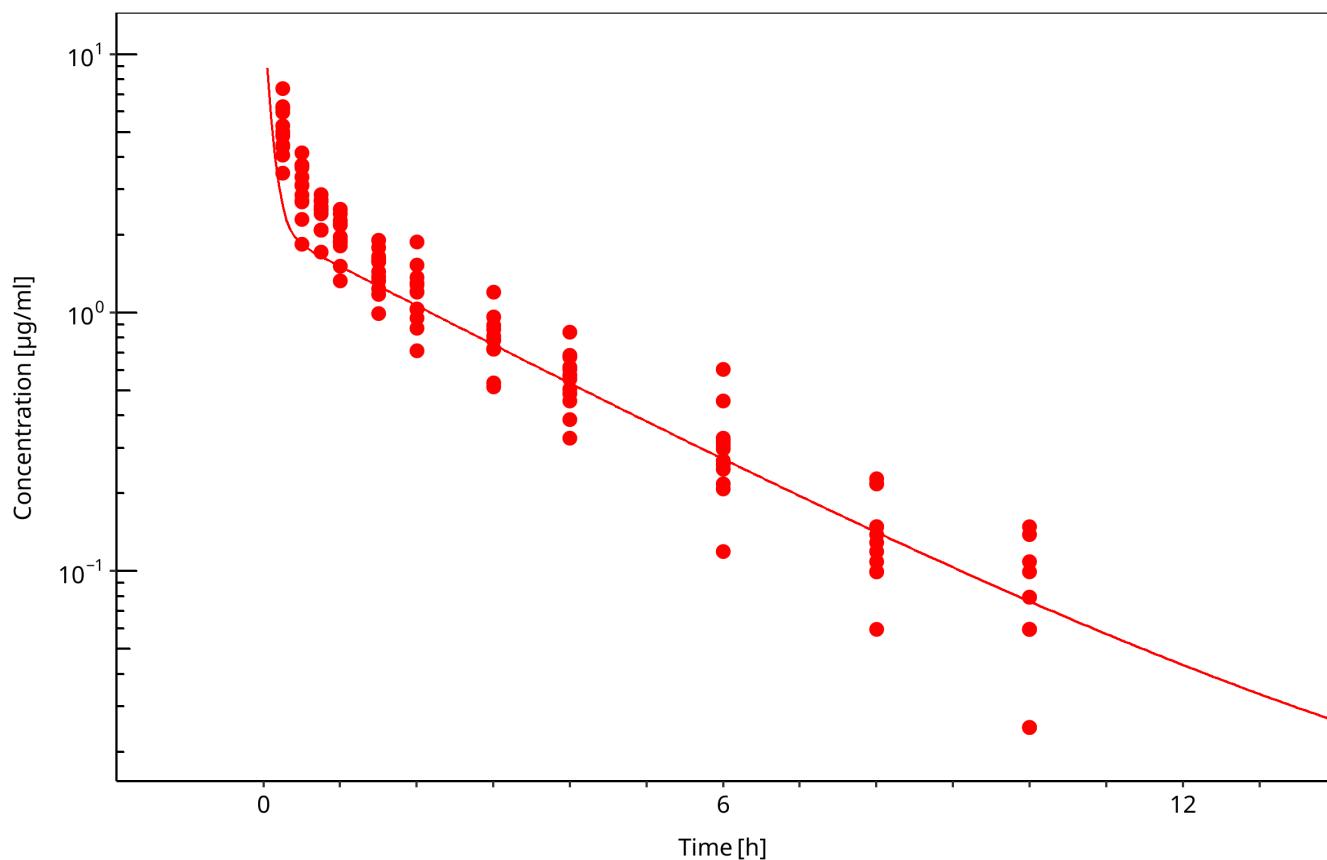
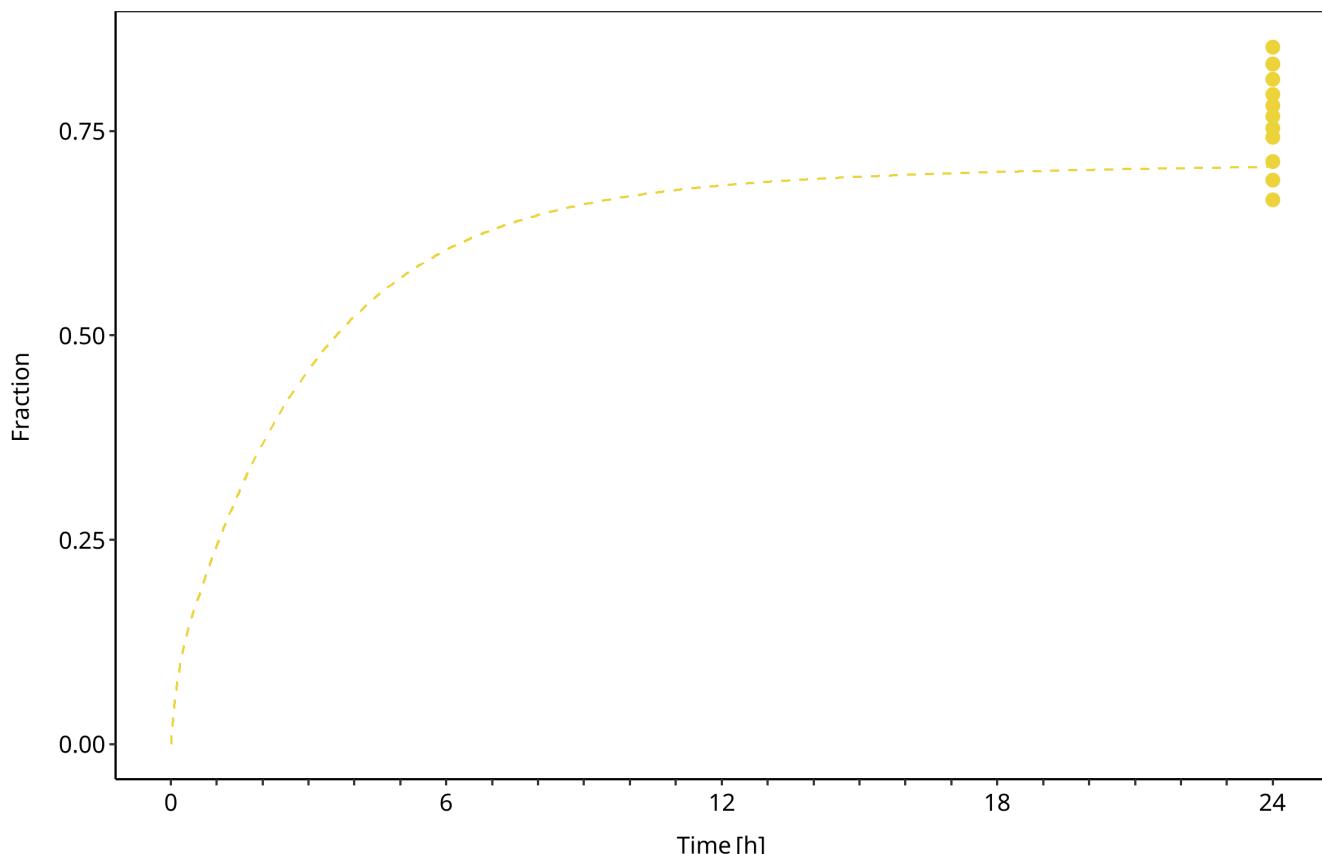
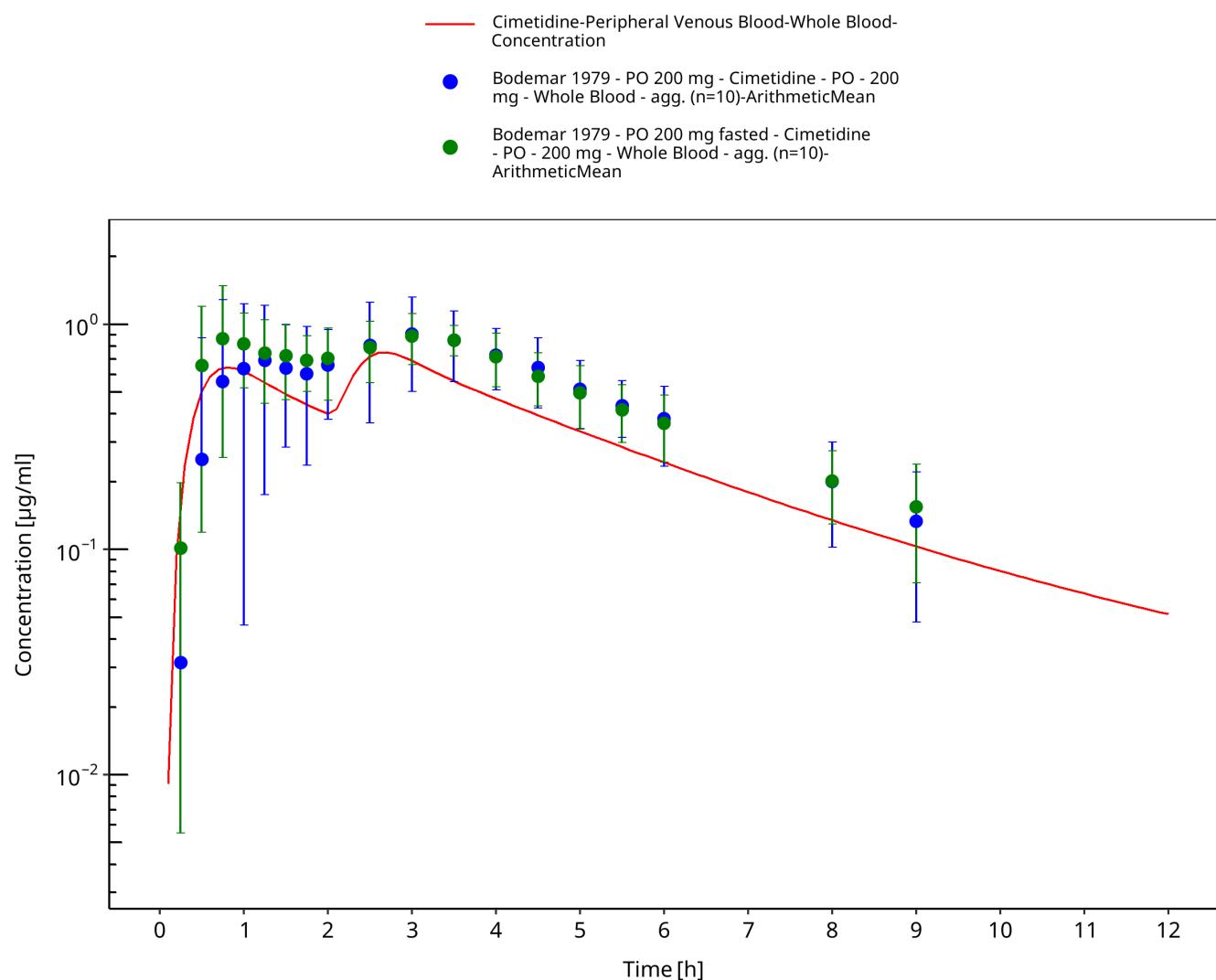


Figure 3-22: iv 300 mg (2 min), Walkenstein 1978, n=12

- Cimetidine-Kidney-Urine-Fraction excreted to urine  
● Walkenstein 1978 - IV 300 mg urine Subject 1  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 10  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 11  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 12  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 2  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 3  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 4  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 5  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 6  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 7  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 8  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual  
● Walkenstein 1978 - IV 300 mg urine Subject 9  
 - Cimetidine - IV - 300 mg - Urine - indiv.-  
 Cimetidine-Kidney-Urine-Individual



**Figure 3-23: iv 300 mg (2 min), Walkenstein 1978, n=12**



**Figure 3-24: po 200 mg (tab), Bodemar 1979 (fasted)**

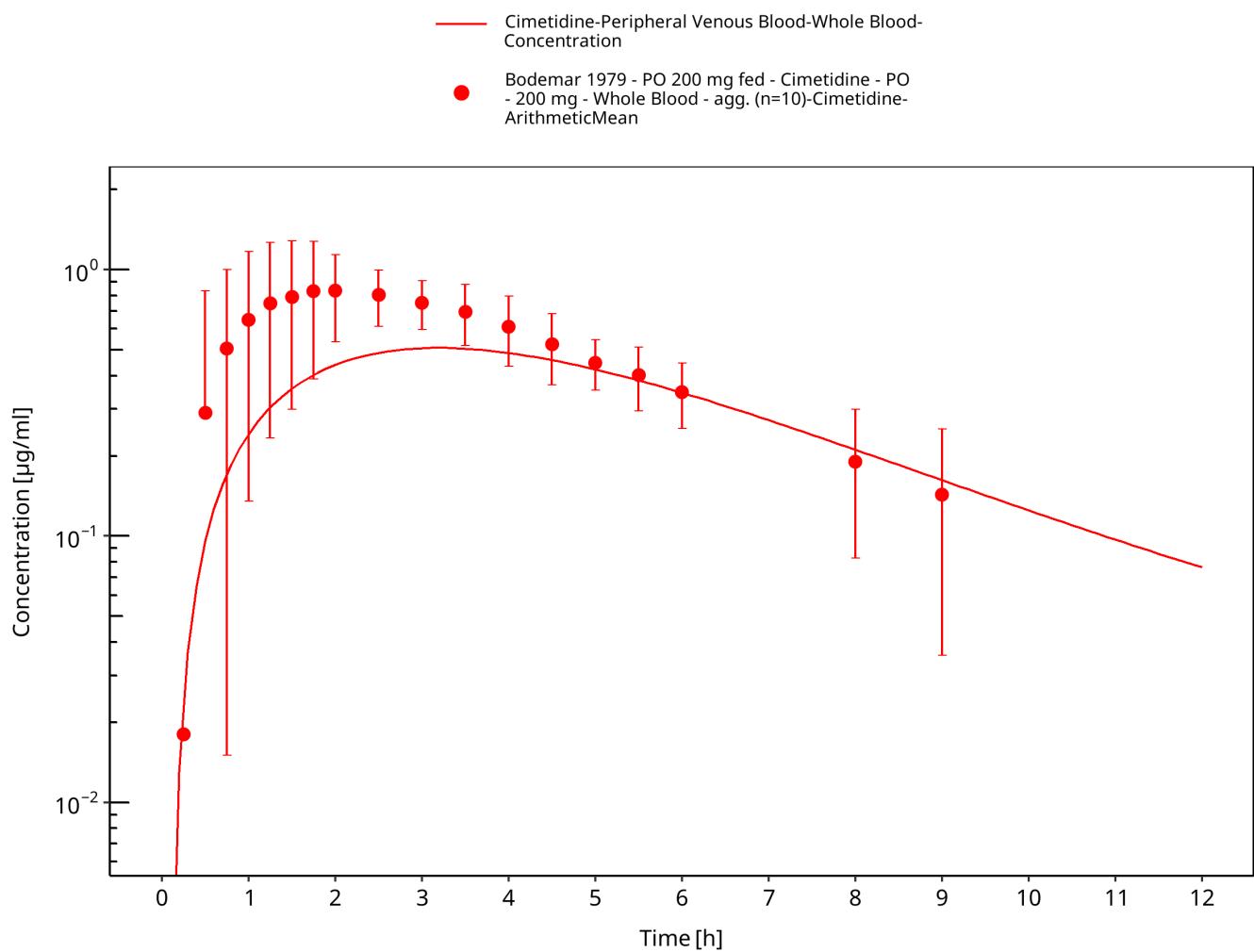


Figure 3-25: po 200 mg (tab), Bodemar 1979 (fed)

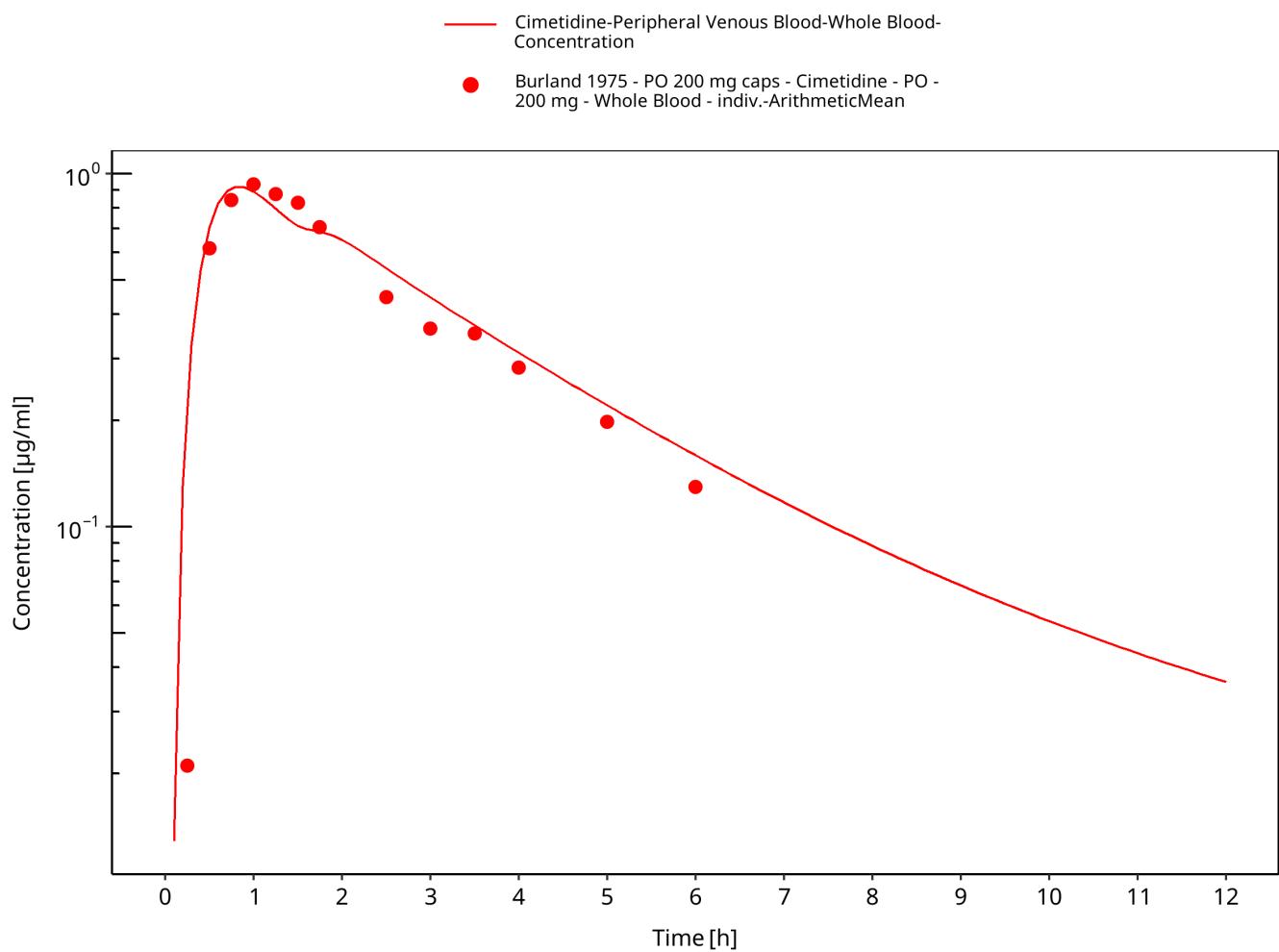


Figure 3-26: po 200 mg, Burland 1975, caps

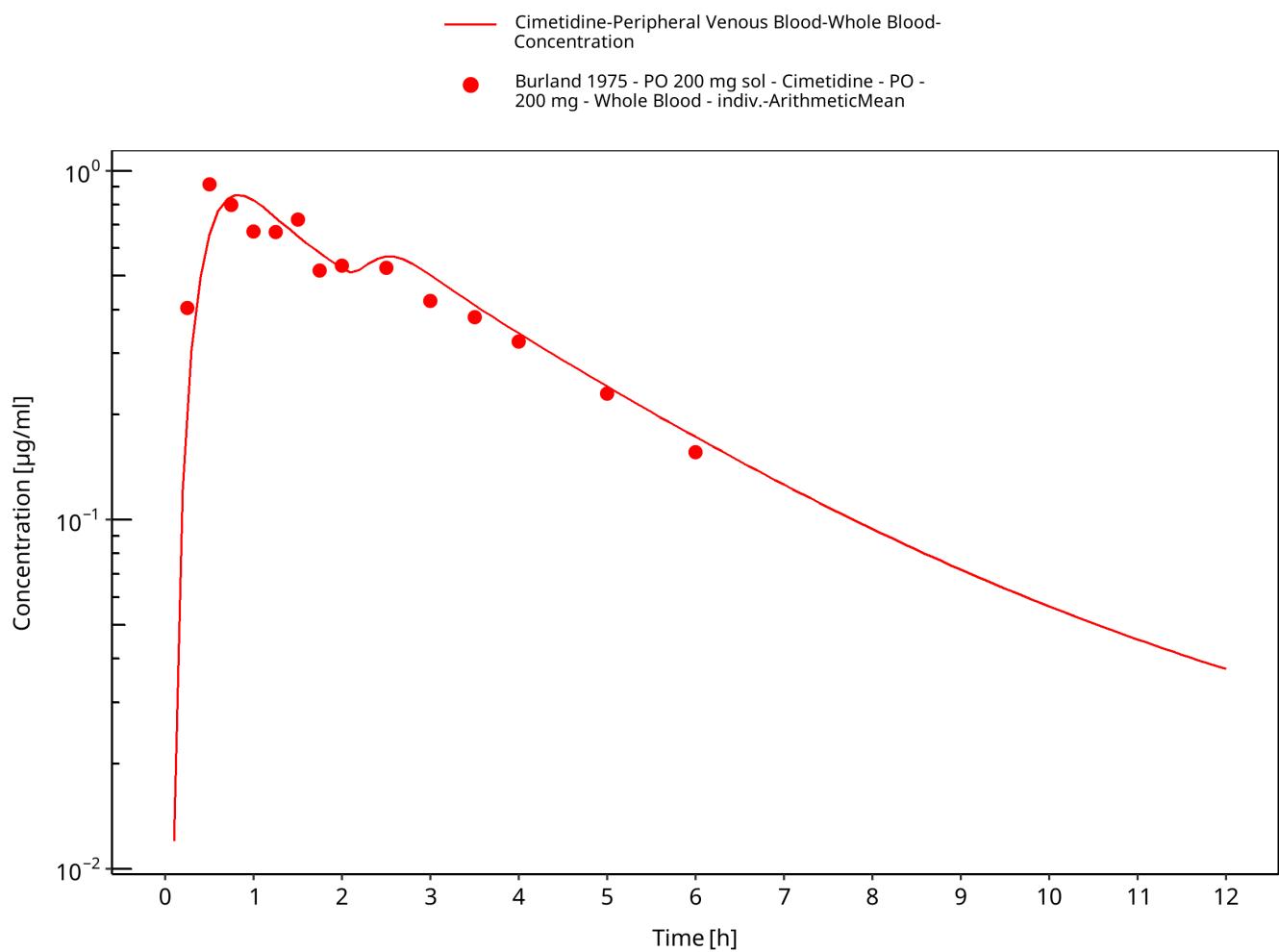


Figure 3-27: po 200 mg, Burland 1975, sol

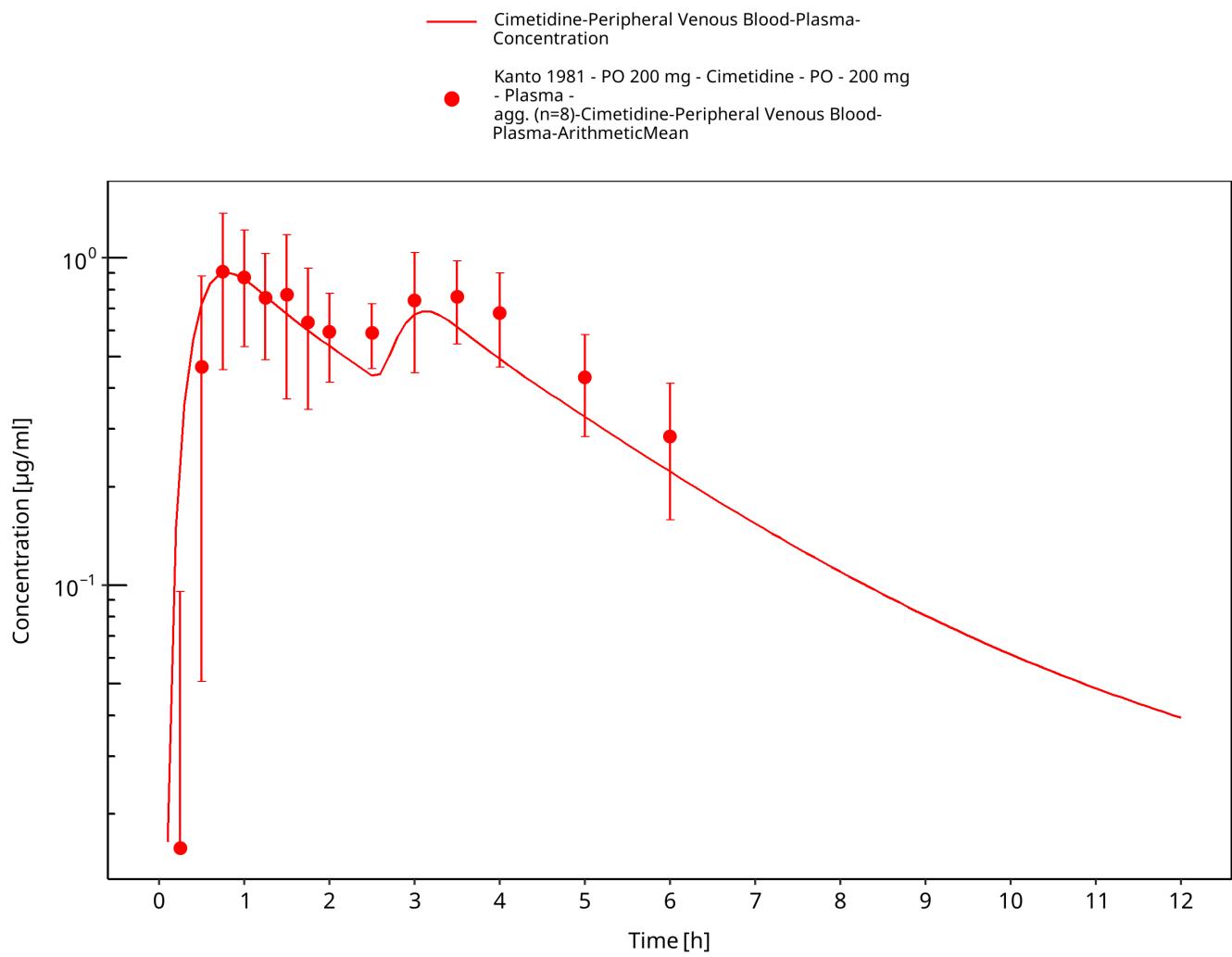


Figure 3-28: po 200 mg, Kanto 1981, n=8

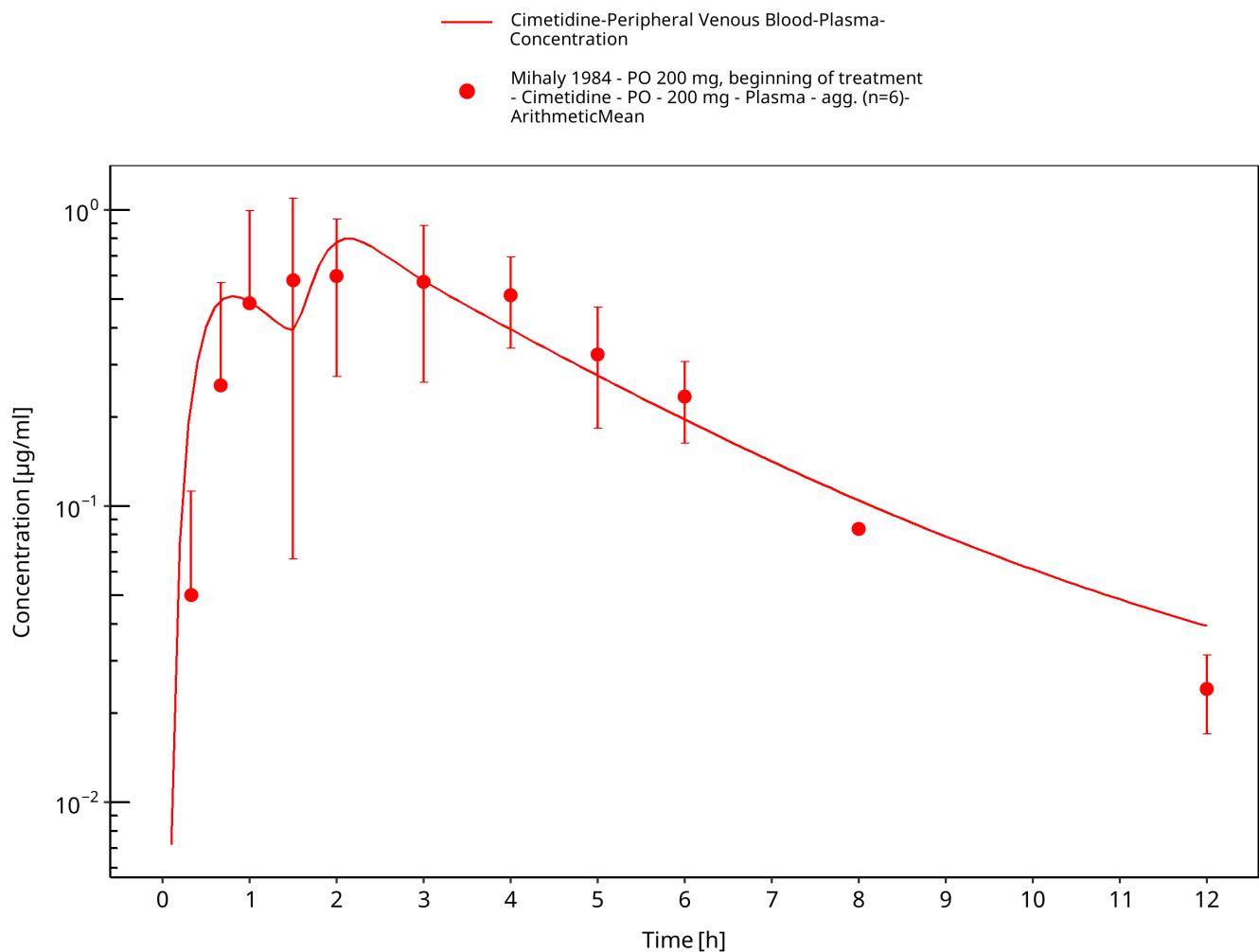


Figure 3-29: po 200 mg, Mihaly 1984, n=8

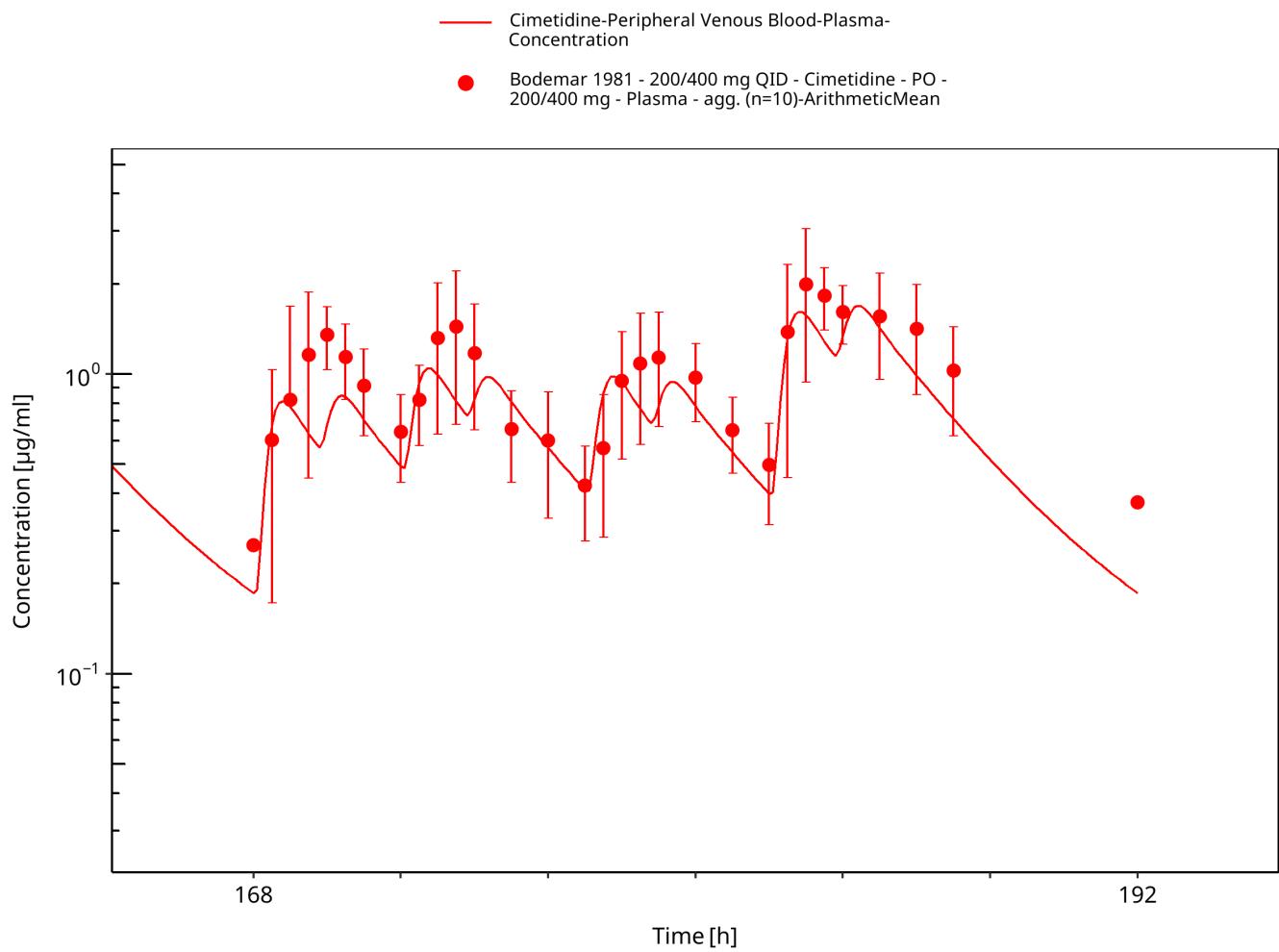
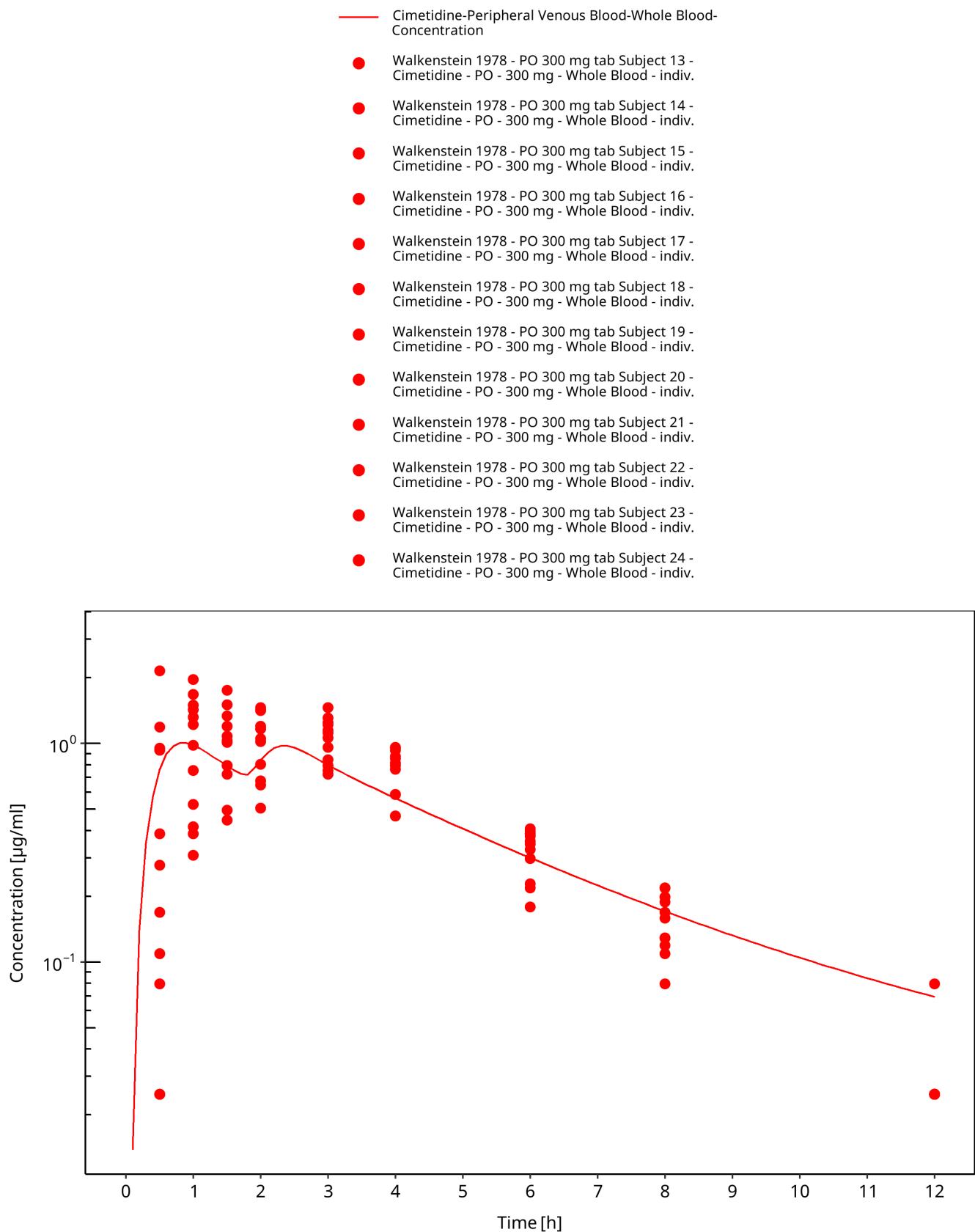


Figure 3-30: po 200/400 mg QID, Bodemar 1981 (fasted)



**Figure 3-31: po 300 mg (tabl), Walkenstein 1978, n=12**

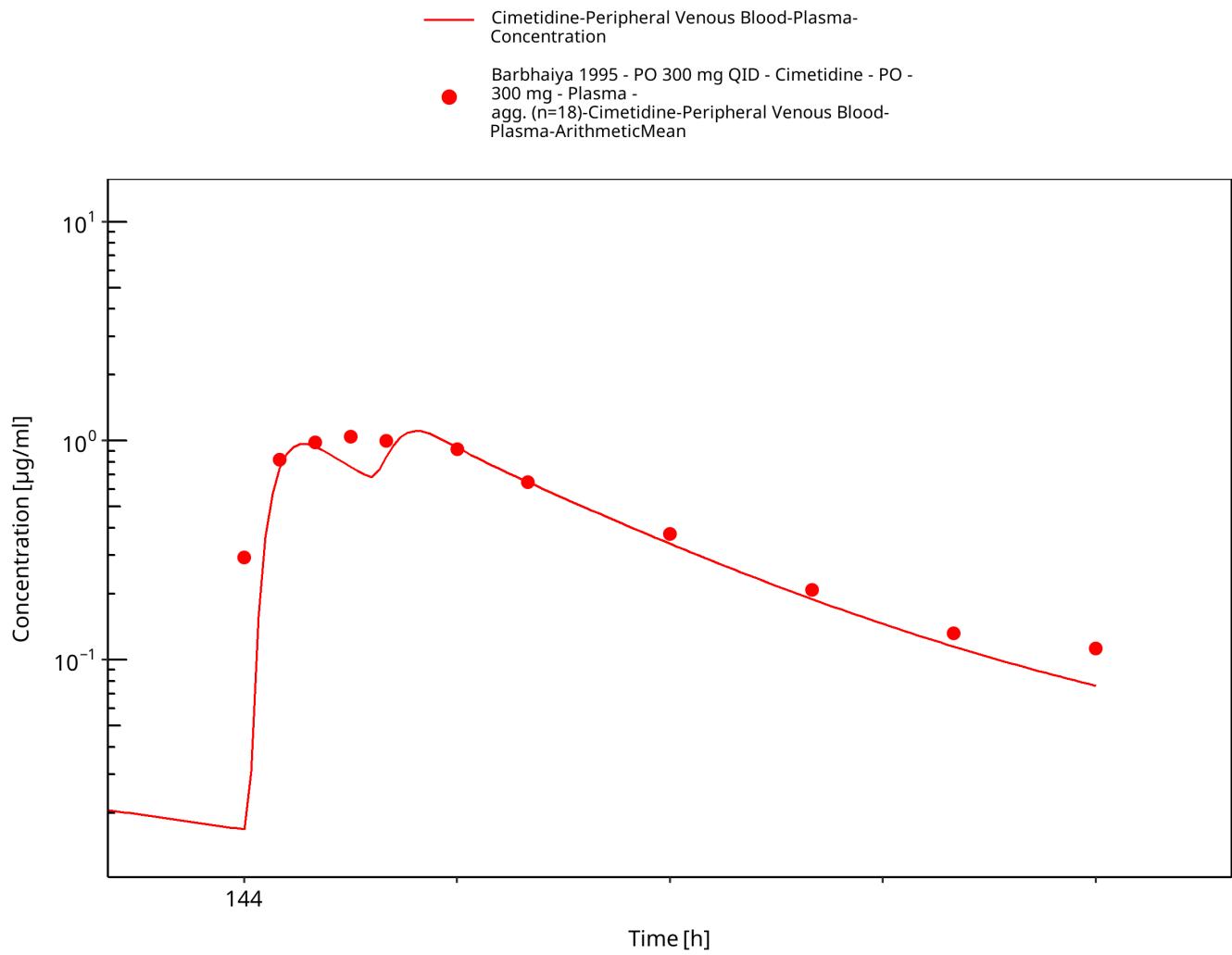


Figure 3-32: po 300 mg QID (sol), Barbhaiya 1995, n=18

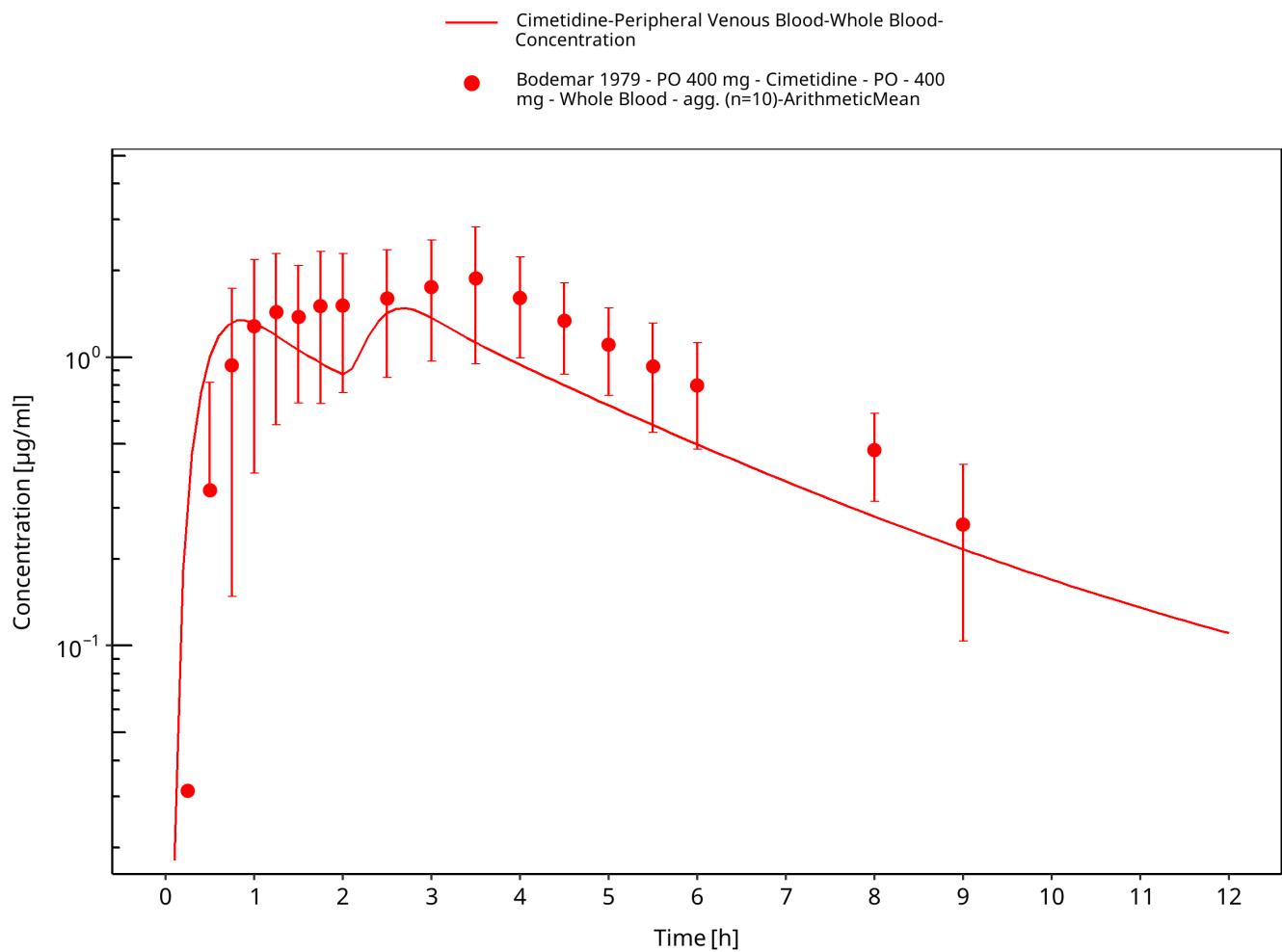


Figure 3-33: po 400 mg (tab), Bodemar 1979, n=10

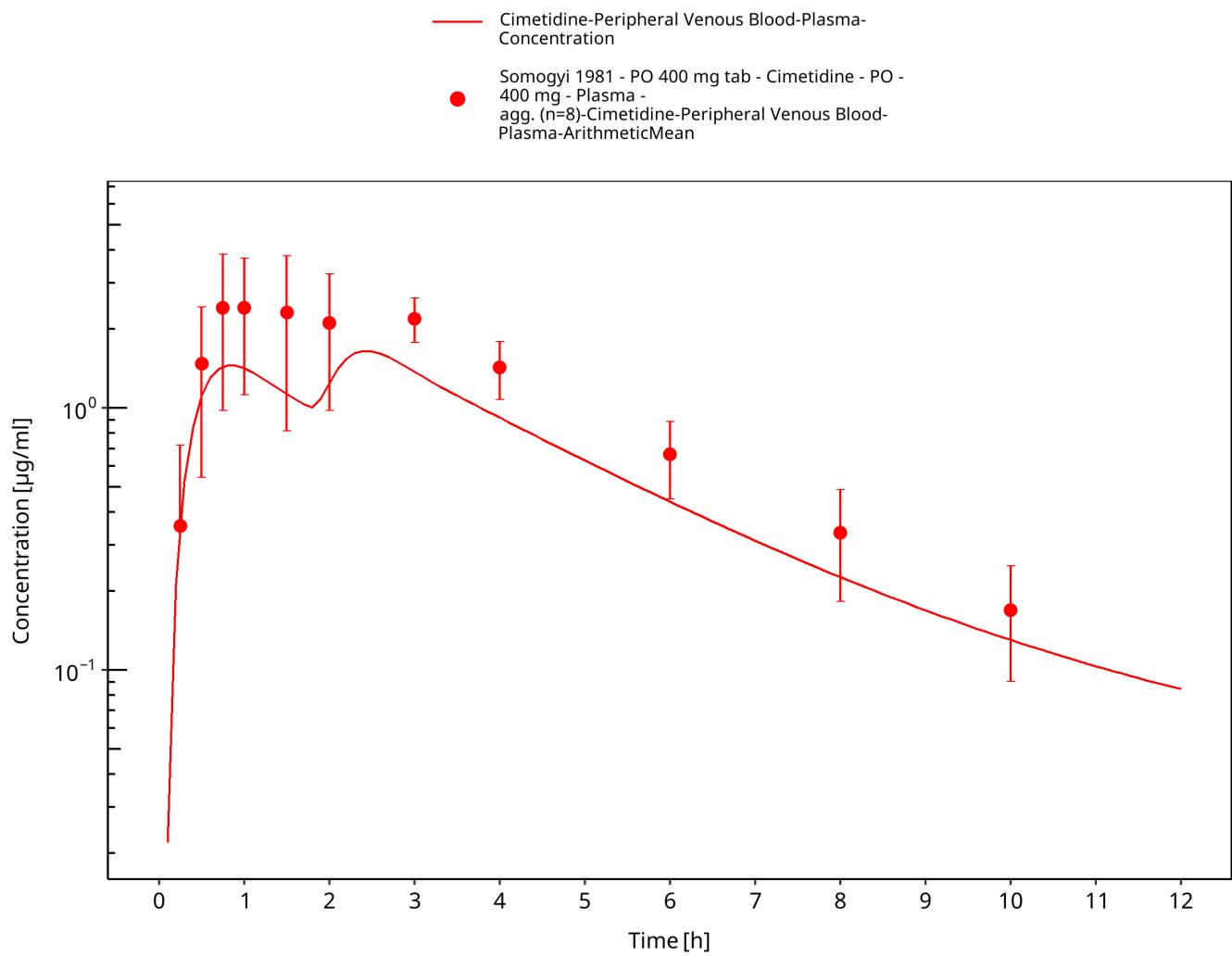


Figure 3-34: po 400 mg (tab), Somogyi 1981, n=8

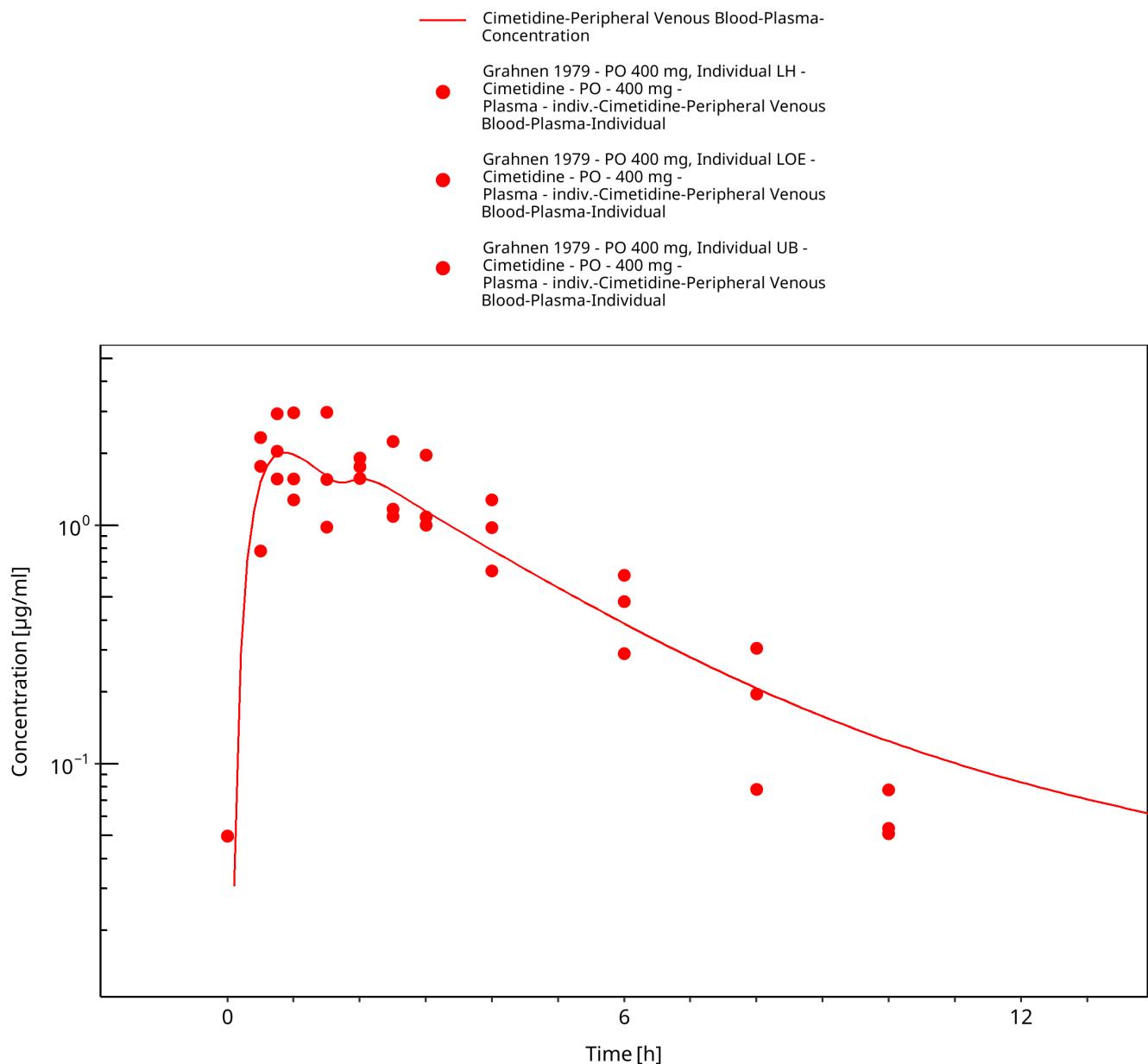


Figure 3-35: po 400 mg (tab),Grahnen 1979, n=3

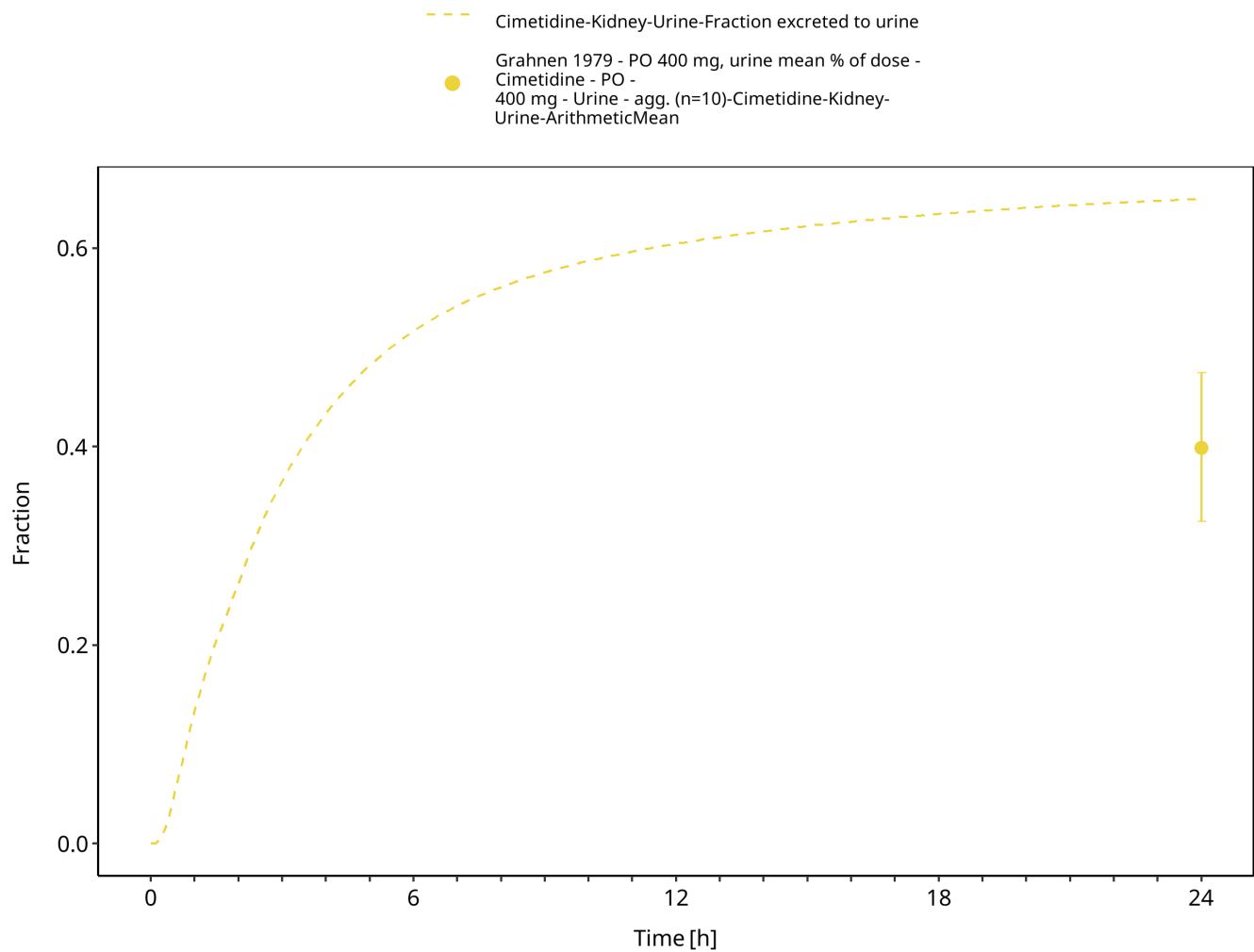


Figure 3-36: po 400 mg (tab),Grahnen 1979, n=3, urine

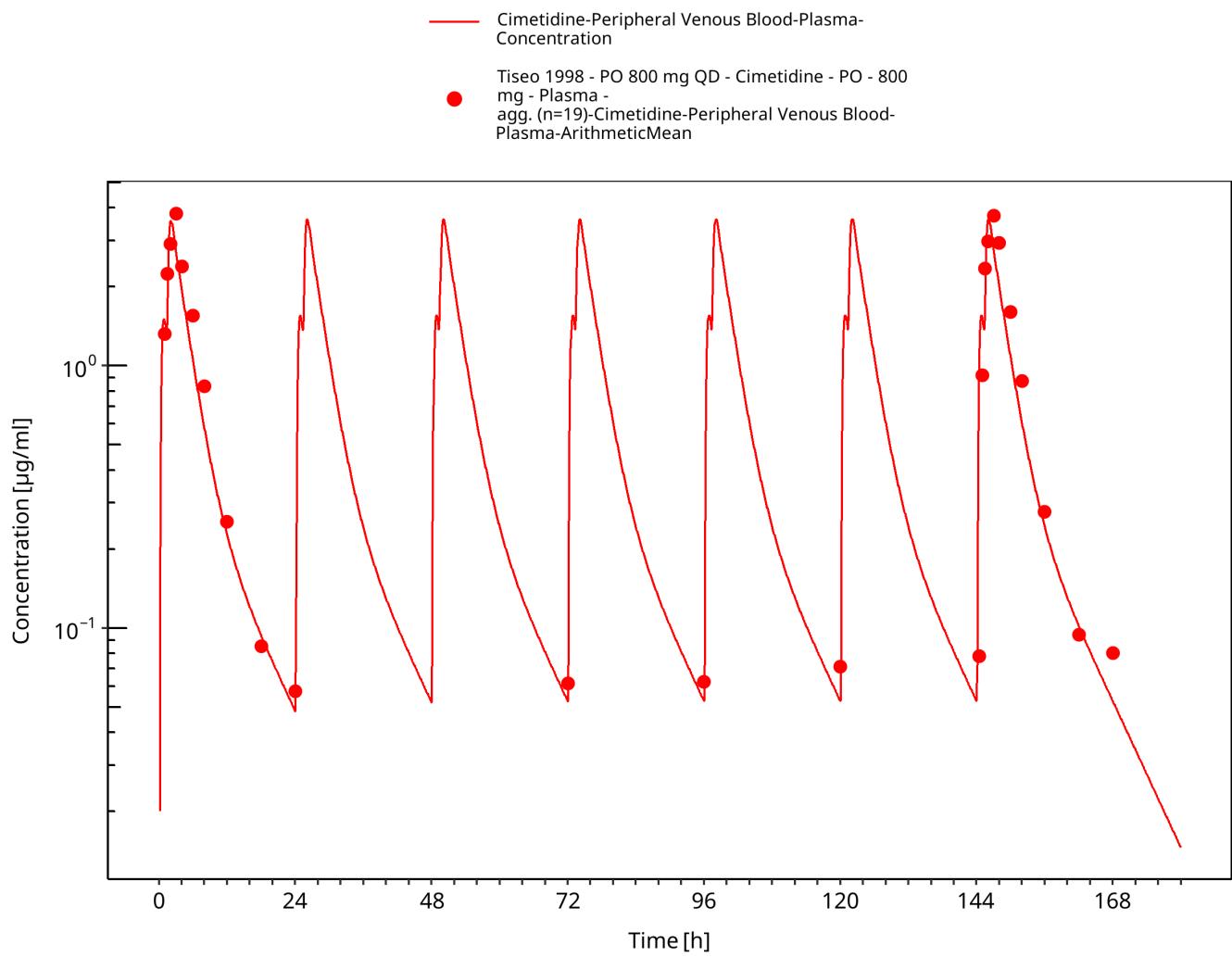


Figure 3-37: po 800 mg (tab) qd, Tiseo 1998, n=18

## 4 Conclusion

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The herein presented PBPK model adequately describes the pharmacokinetics of cimetidine after intravenous and oral administration of single and multiple doses to healthy adults and peptic ulcer patients covering a broad dosing range from 100 to 800 mg. The established cimetidine PBPK model is verified for the use as a mild inhibitor of CYP3A4 drug in drug-drug interaction simulations.

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