

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

| | |
|---|---|
| Version | 2.0-OSP12.1 |
| based on <i>Model Snapshot</i> and <i>Evaluation Plan</i> | https://github.com/Open-Systems-Pharmacology/Cimetidine-Model/releases/tag/v2.0 |
| OSP Version | 12.1 |
| Qualification Framework Version | 3.3 |

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

Cimetidine is a histamine H₂ 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_i and MATE1 K_i.

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

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

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 _a 1 | | 6.93 (base) | Avdeef 2001 | Acid dissociation constant |
| pK _a 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 _u | % | 78.00 | Taylor 1978 | Fraction unbound in plasma |
| B/P ratio | | 0.98 | Somogyi 1983 | Blood to plasma ratio |
| OCT1 K _m | μmol/l | 2600 | Umeshara 2007 | Michaelis-Menten constant |
| OAT3 K _m | μmol/l | 149 | Tahara 2005 | Michaelis-Menten constant |
| MATE1 K _m | μmol/l | 8.0 | Ohta 2005 | Michaelis-Menten constant |
| OCT1 K _i | μmol/l | 104 | Ito 2012 | Inhibition constant for competitive inhibition |
| OCT2 K _i | μmol/l | 124 | Ito 2012 | Inhibition constant for competitive inhibition |
| MATE1 K _i (refitted in PK-Sim V10) | μmol/l | 3.8 (0.65) | Ito 2012 | Inhibition constant for competitive inhibition |
| CYP3A4 K _i (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- https://github.com/Open-Systems-Pharmacology/Cimetidine-Metformin-DDI |

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

| Group | GMFE |
|------------------------------|-------------|
| iv administration | 1.36 |
| multiple oral administration | 1.50 |
| single oral administration | 1.51 |
| All | 1.47 |

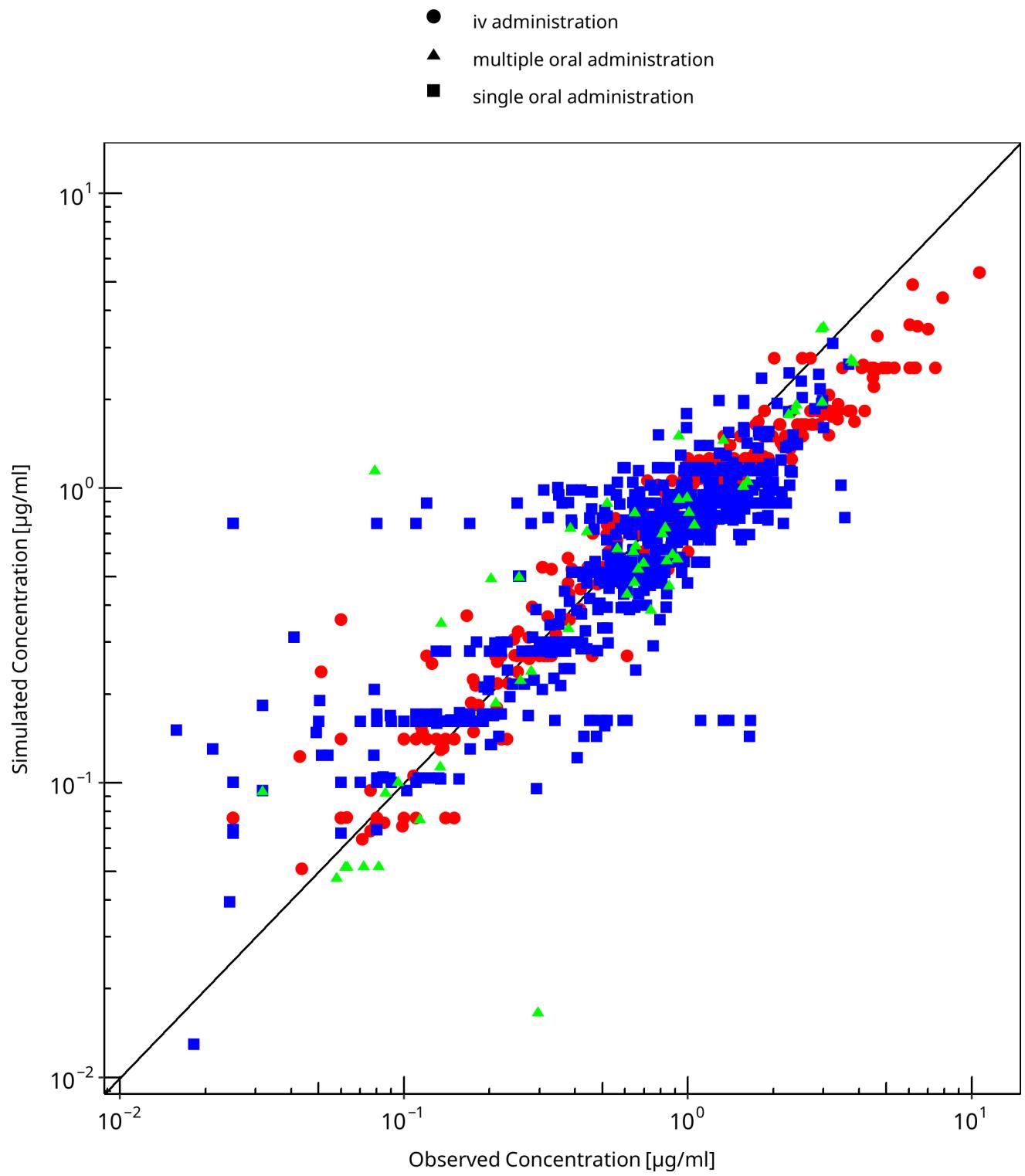


Figure 3-1: Goodness of fit plot for concentration in plasma

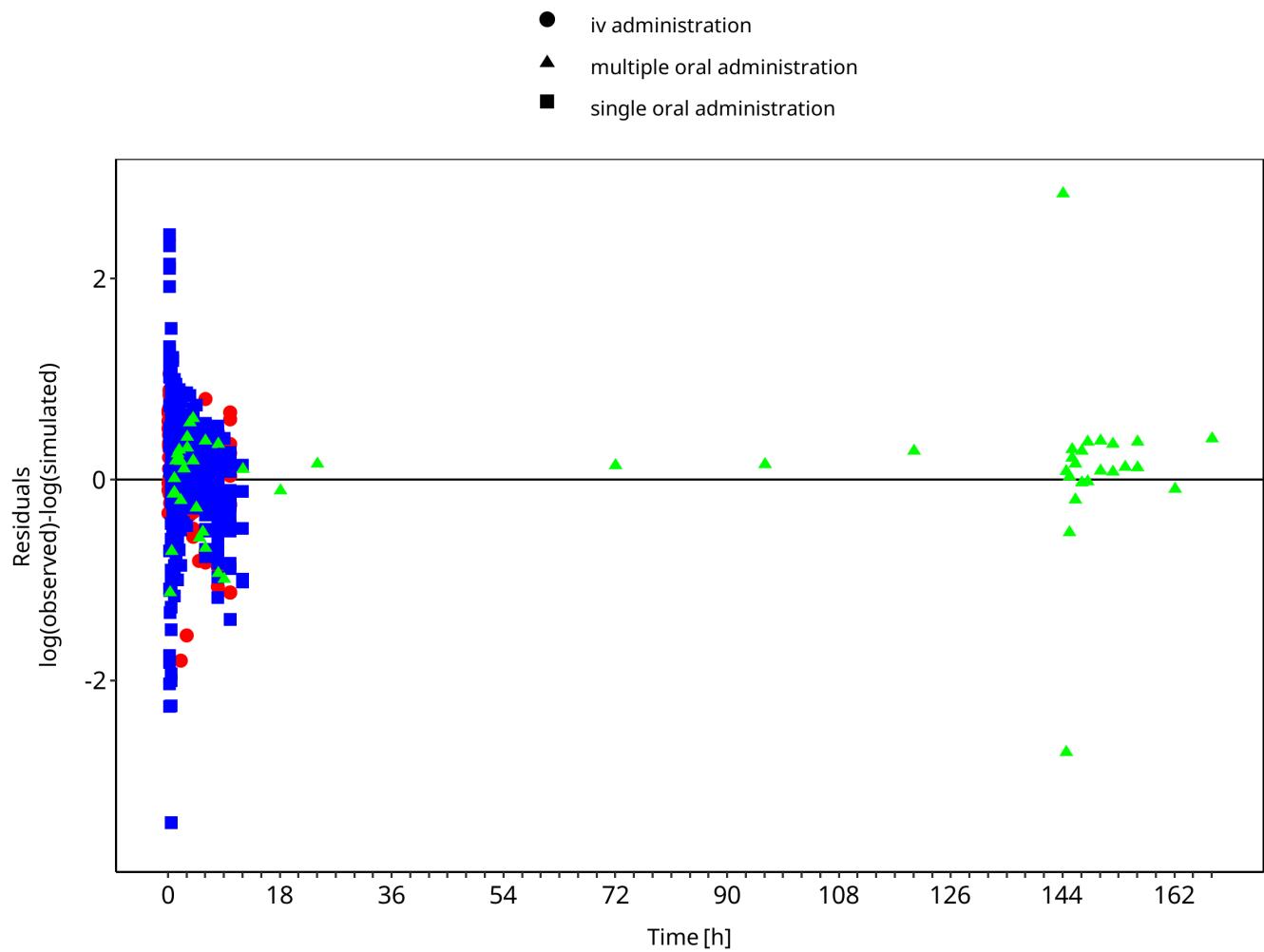


Figure 3-2: Goodness of fit plot for concentration in plasma

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

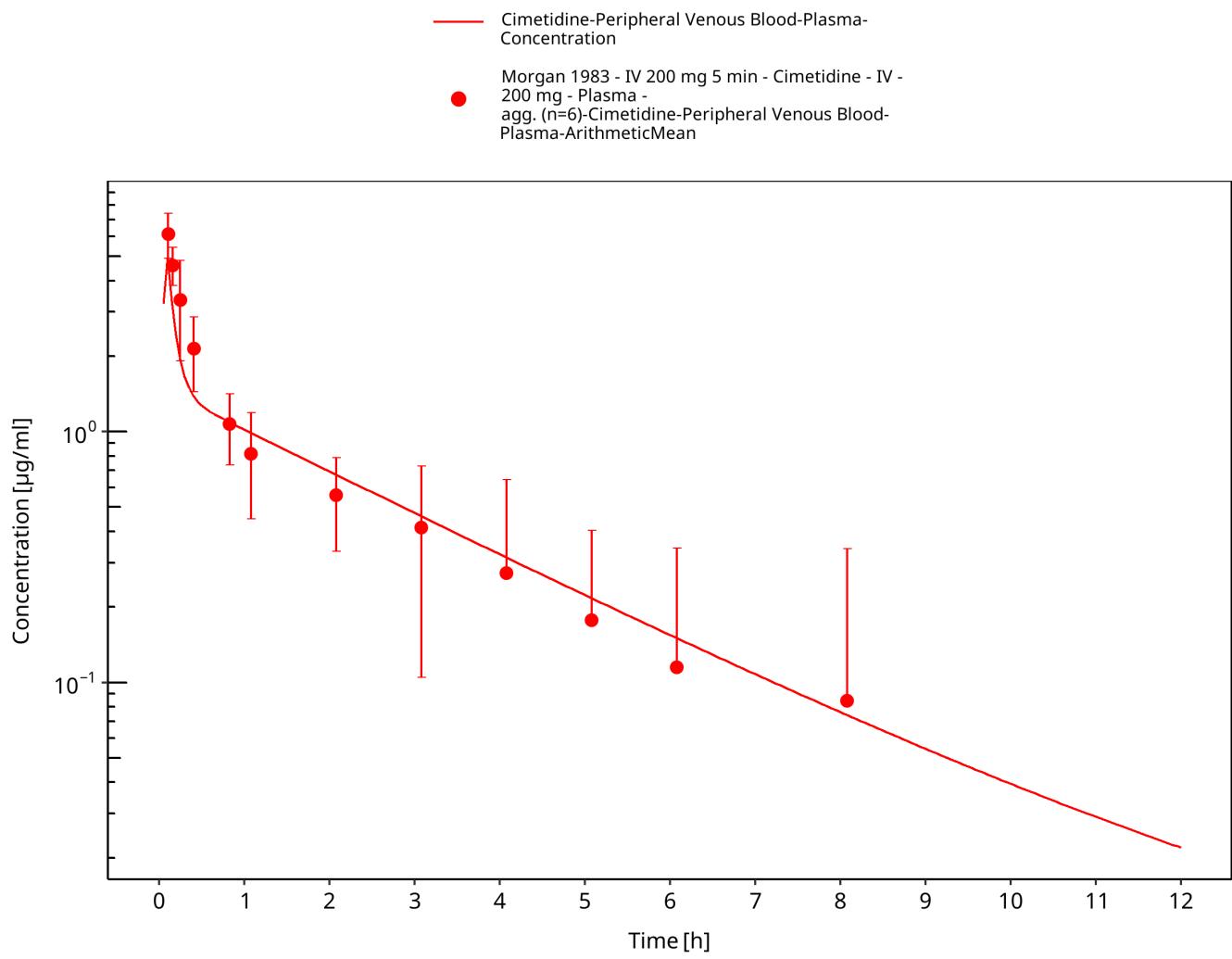


Figure 3-3: iv 200 mg (5 min),Morgan 1983, n=6

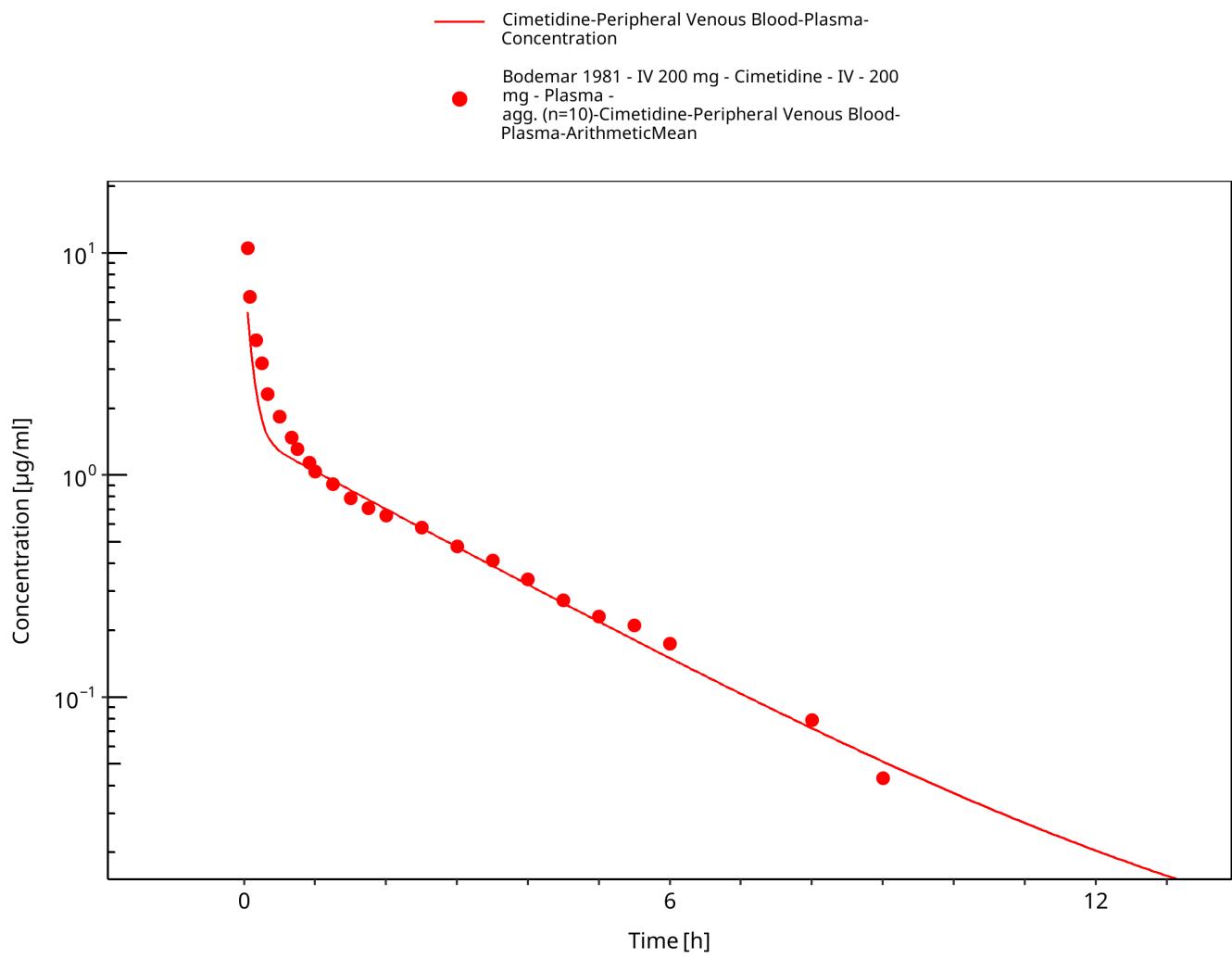


Figure 3-4: iv 200 mg, Bodemar 1981, n=10

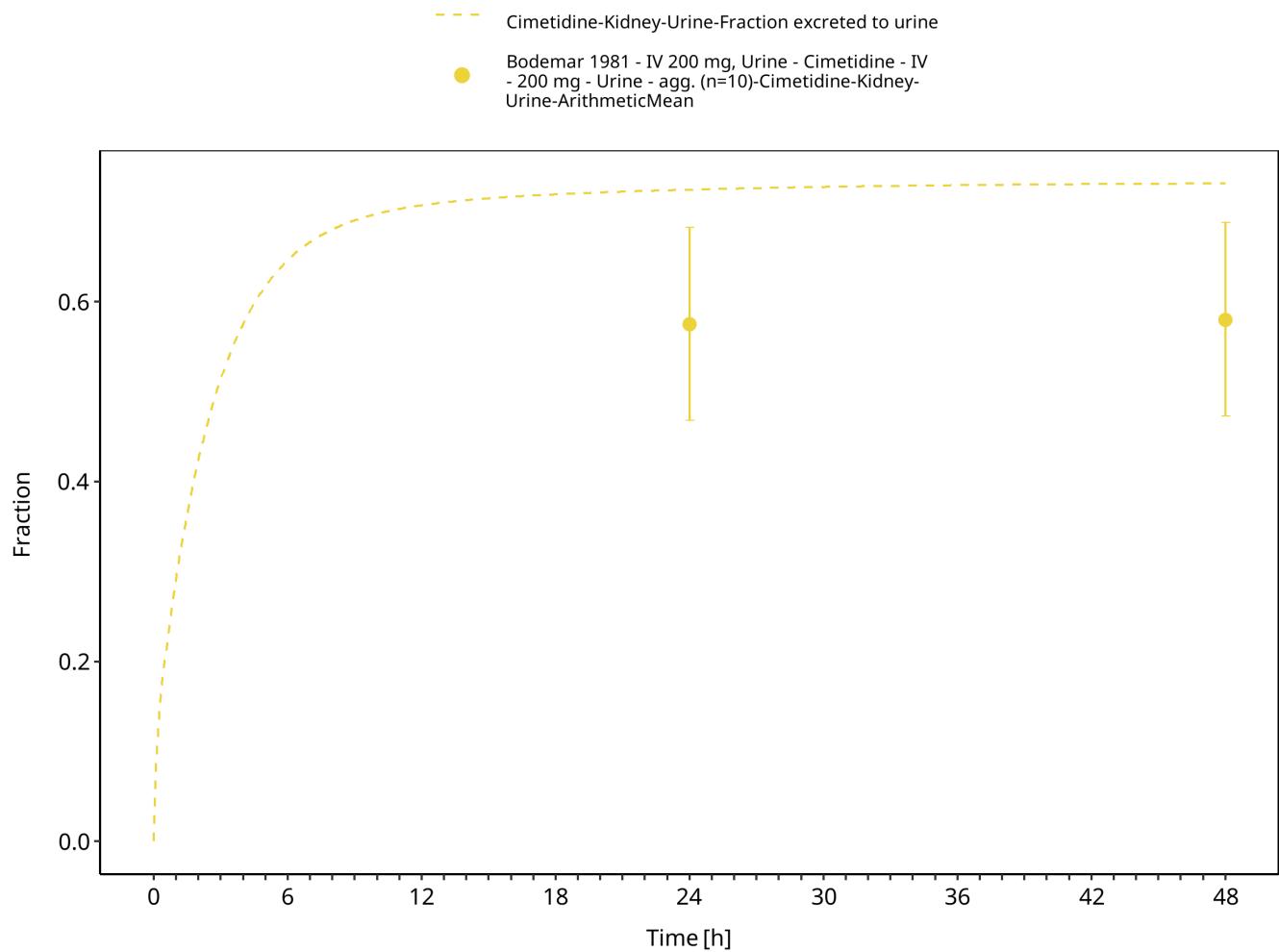


Figure 3-5: iv 200 mg, Bodemar 1981, n=10, urine

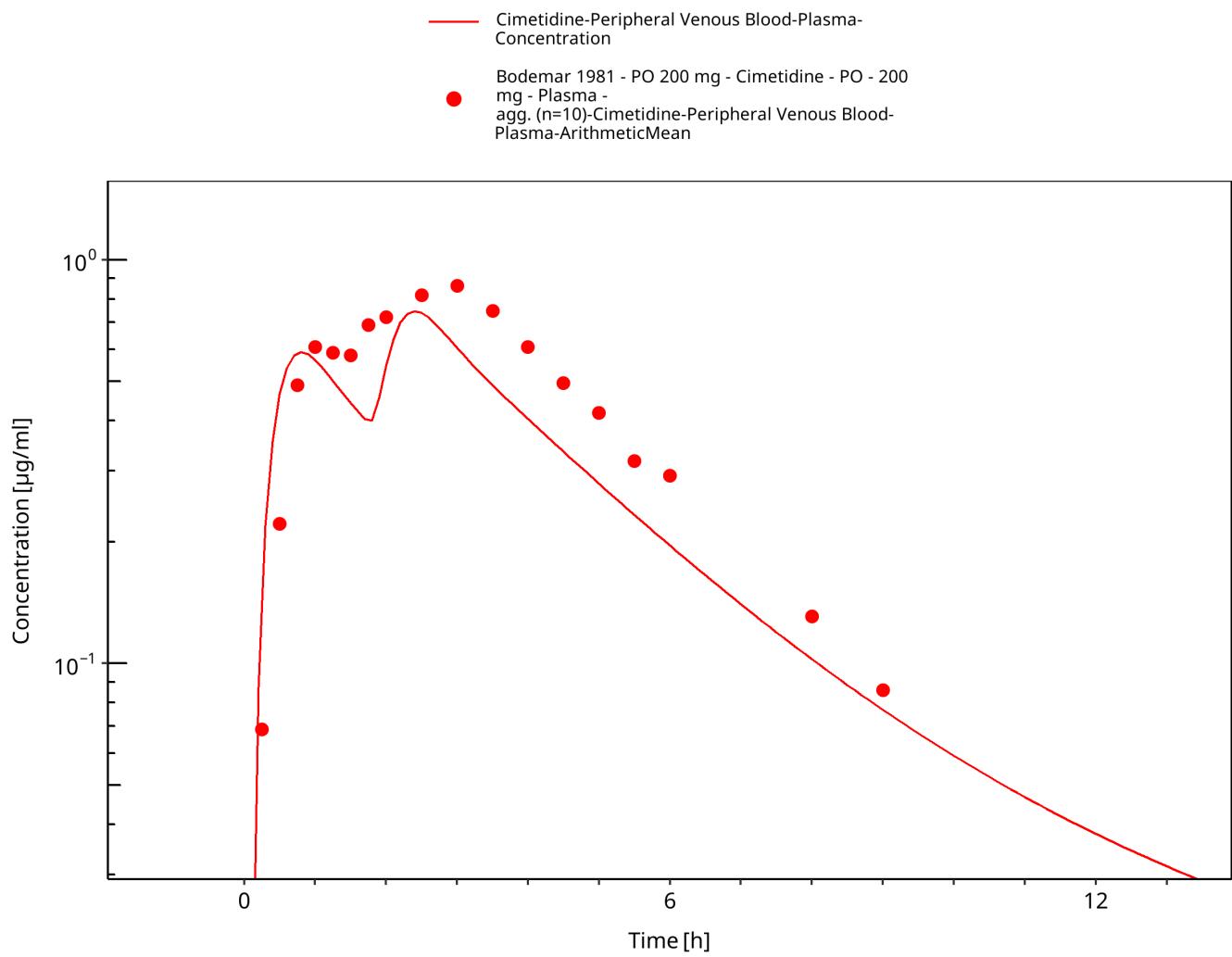


Figure 3-6: po 200 mg, Bodemar 1981, n=10

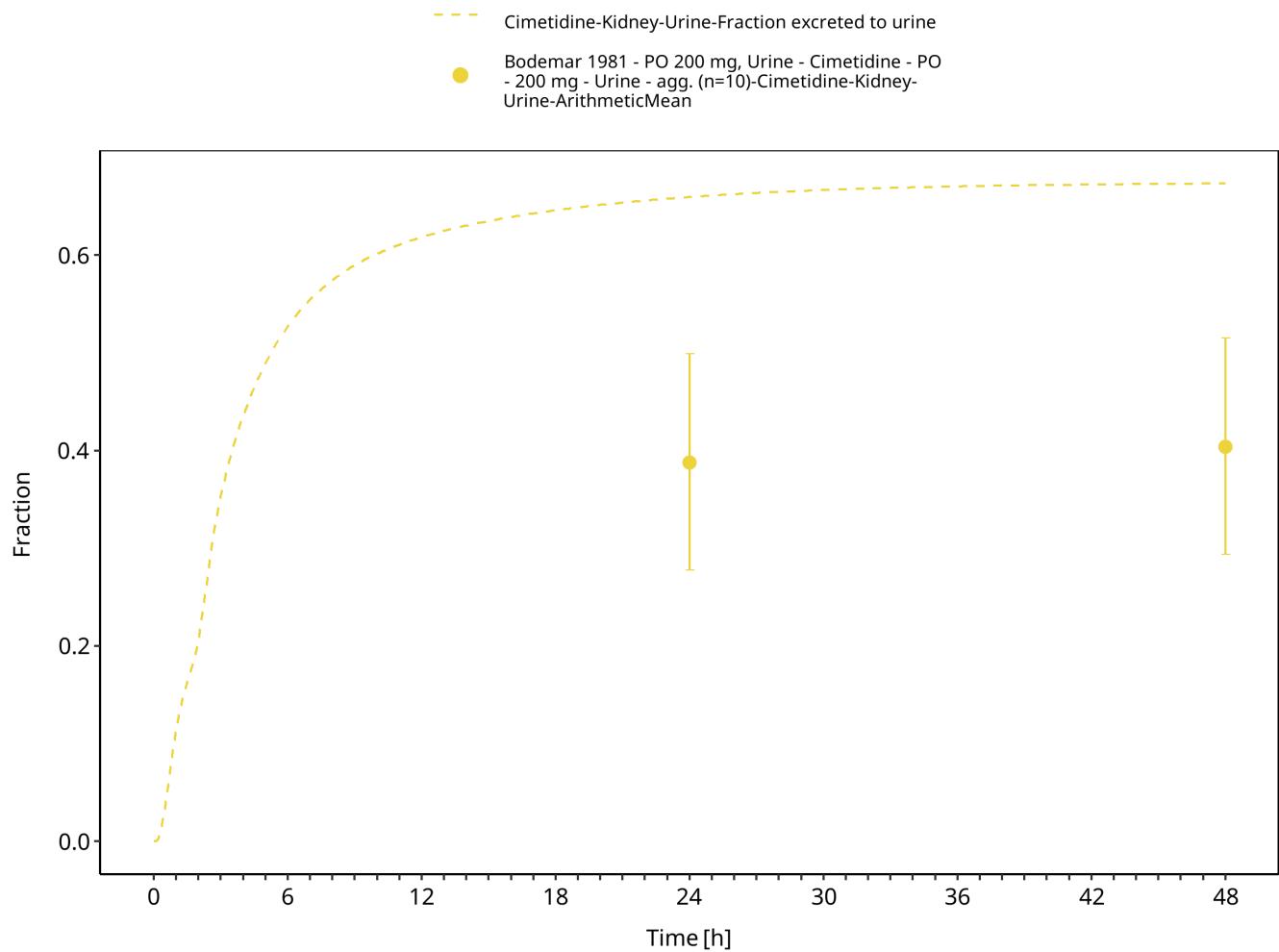


Figure 3-7: po 200 mg, Bodemar 1981, n=10, urine

- 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.

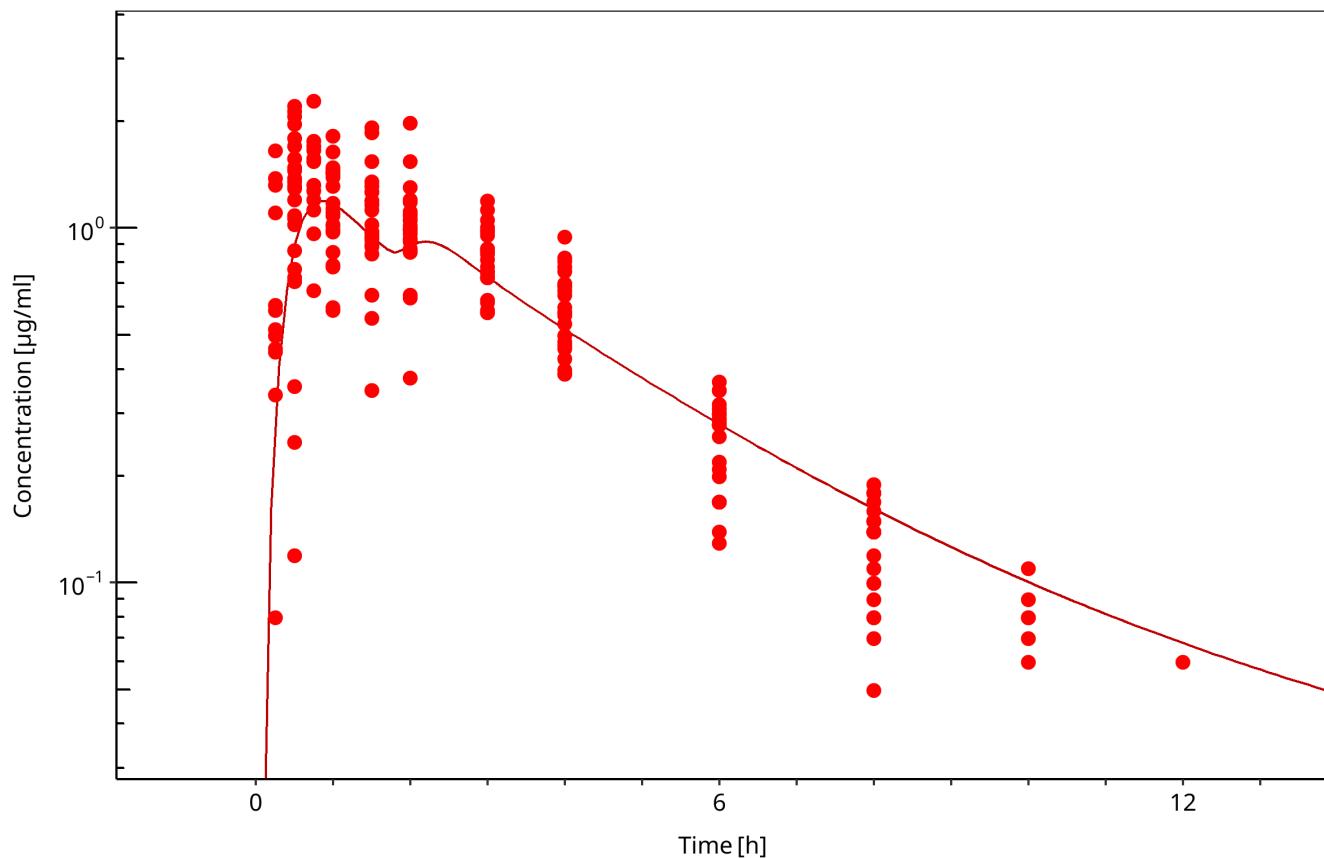


Figure 3-8: po 300 mg (sol), Walkenstein 1978, n=24

- 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

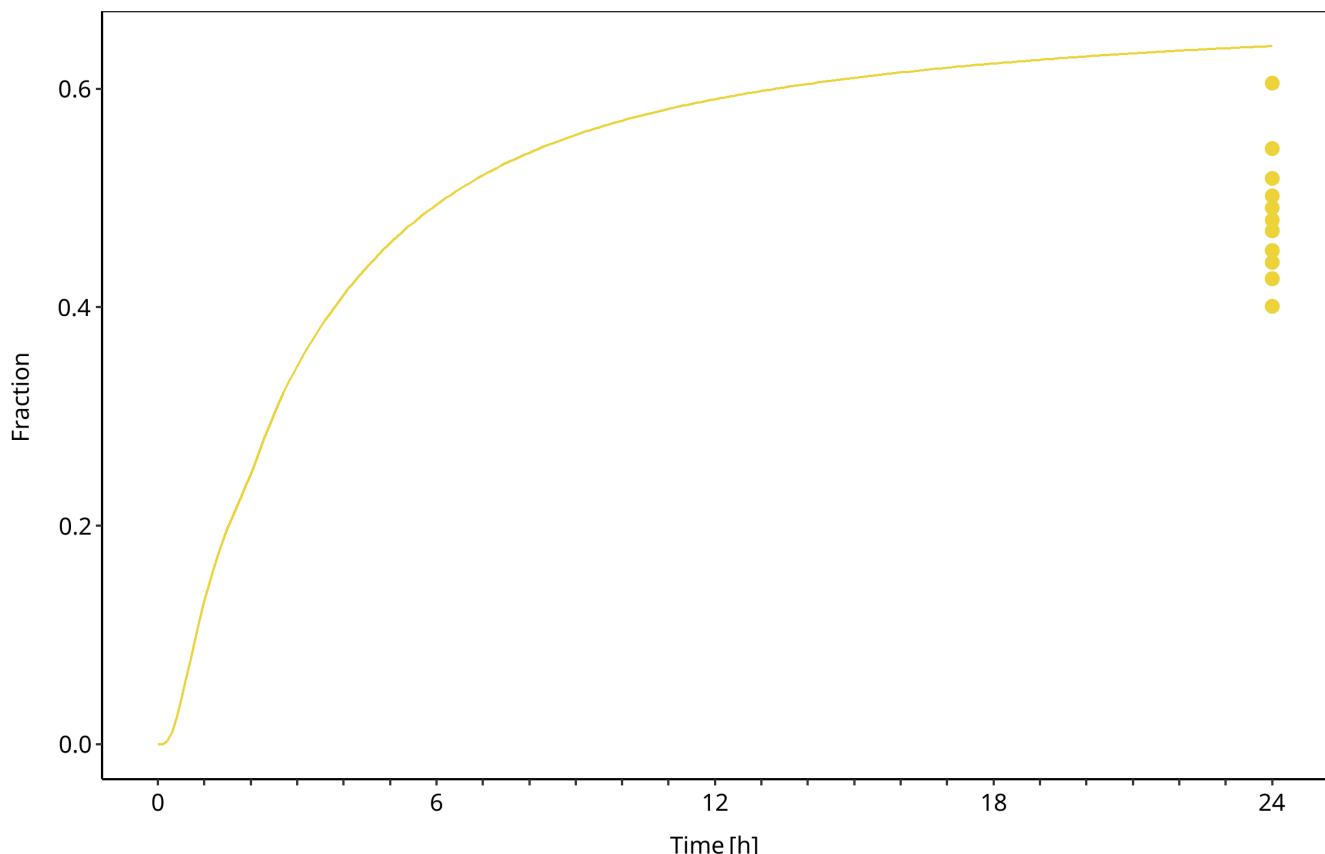


Figure 3-9: po 300 mg (sol), Walkenstein 1978, n=24, urine

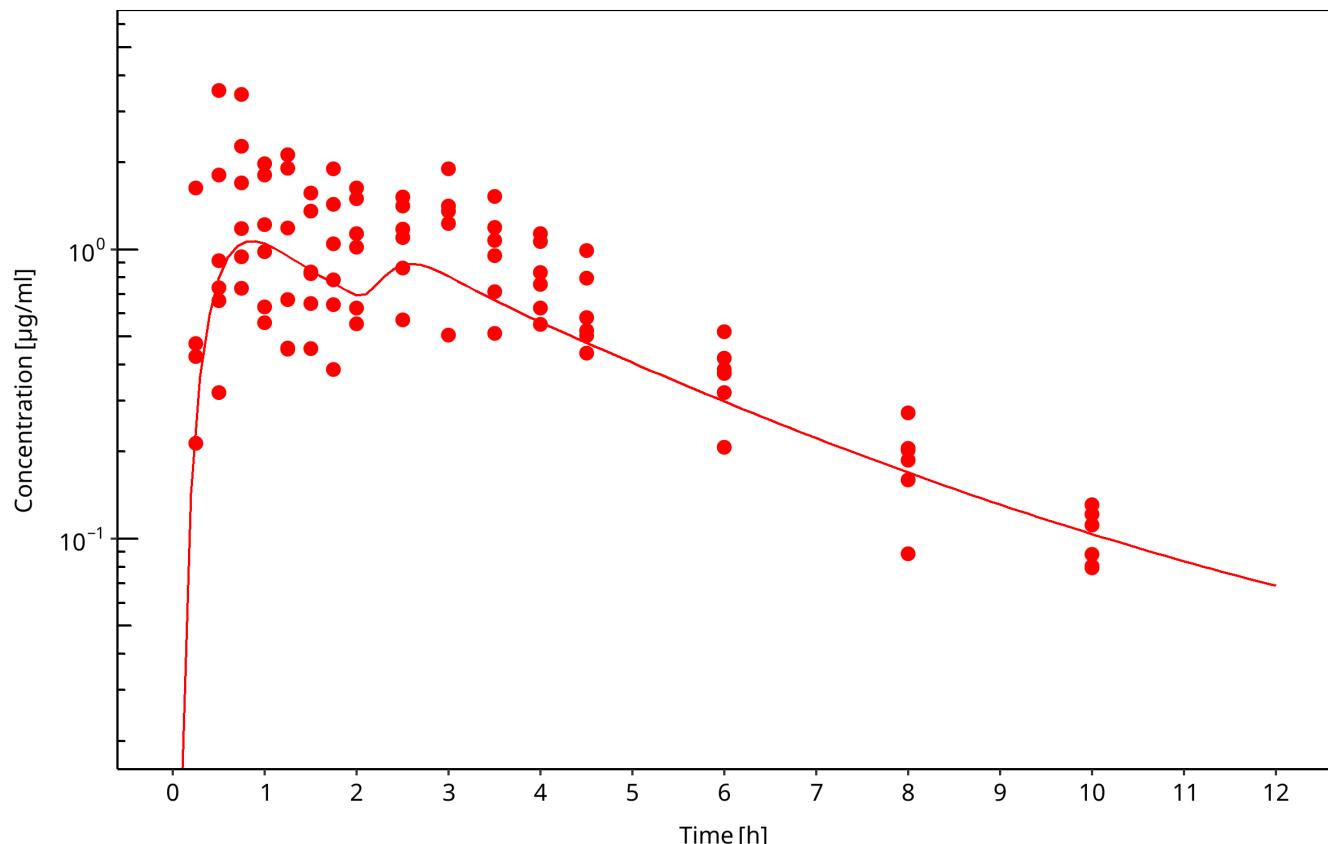
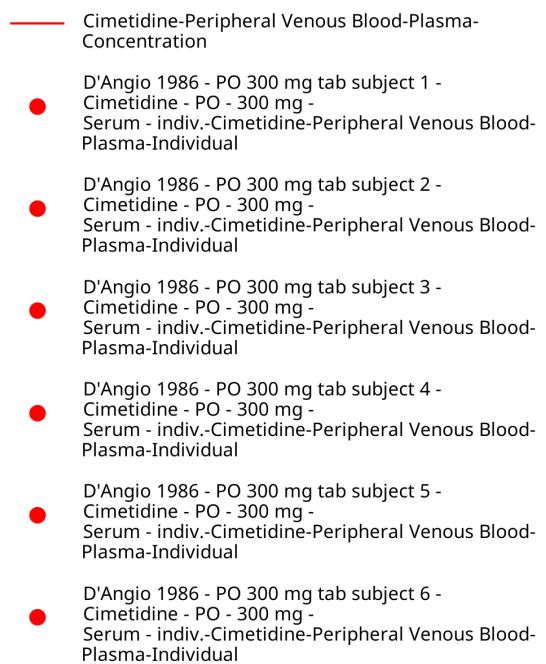


Figure 3-10: po 300 mg (tab), D'Angio 1986, n=6

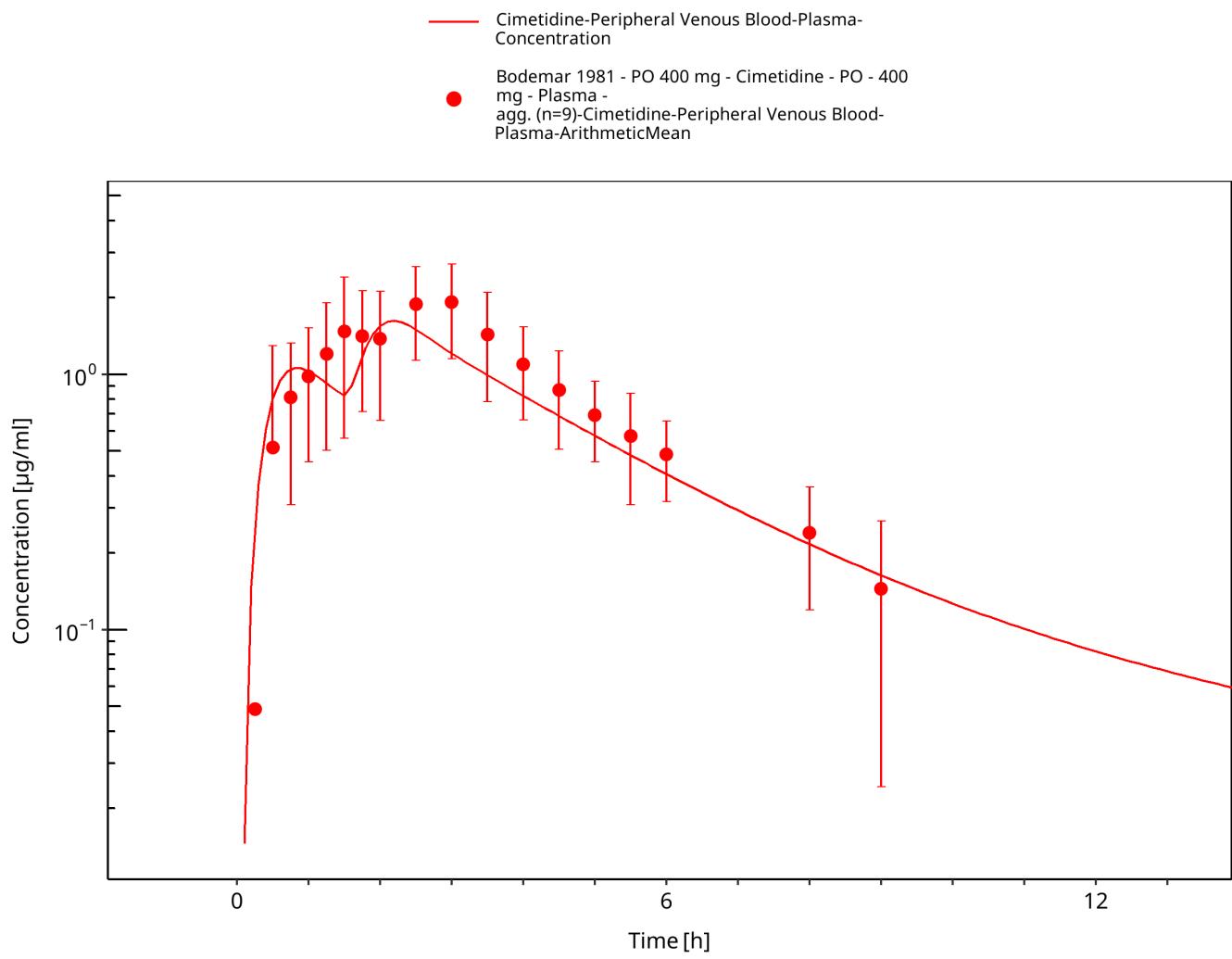


Figure 3-11: po 400 mg, Bodemar 1981, n=9

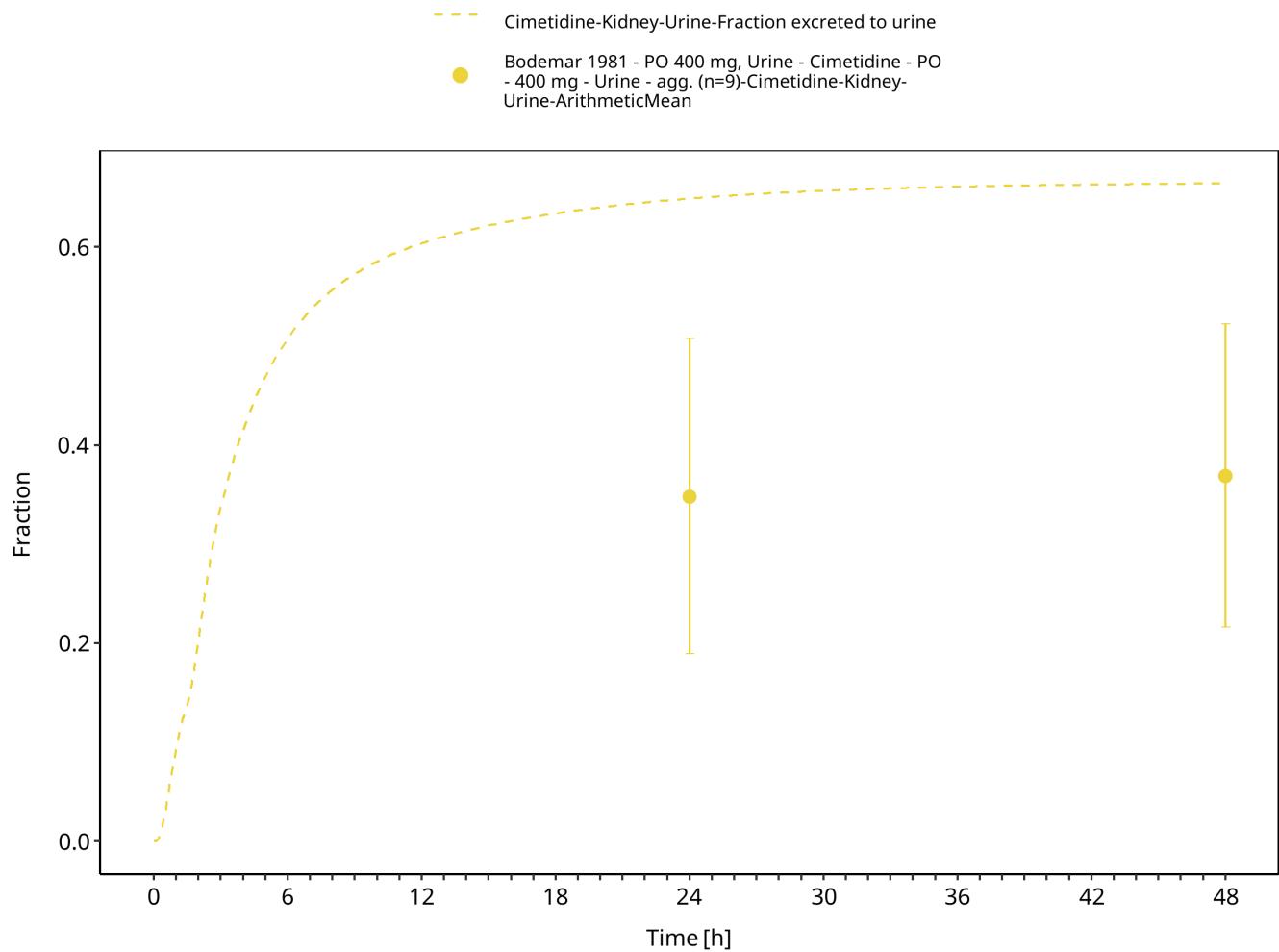


Figure 3-12: po 400 mg, Bodemar 1981, n=9, urine

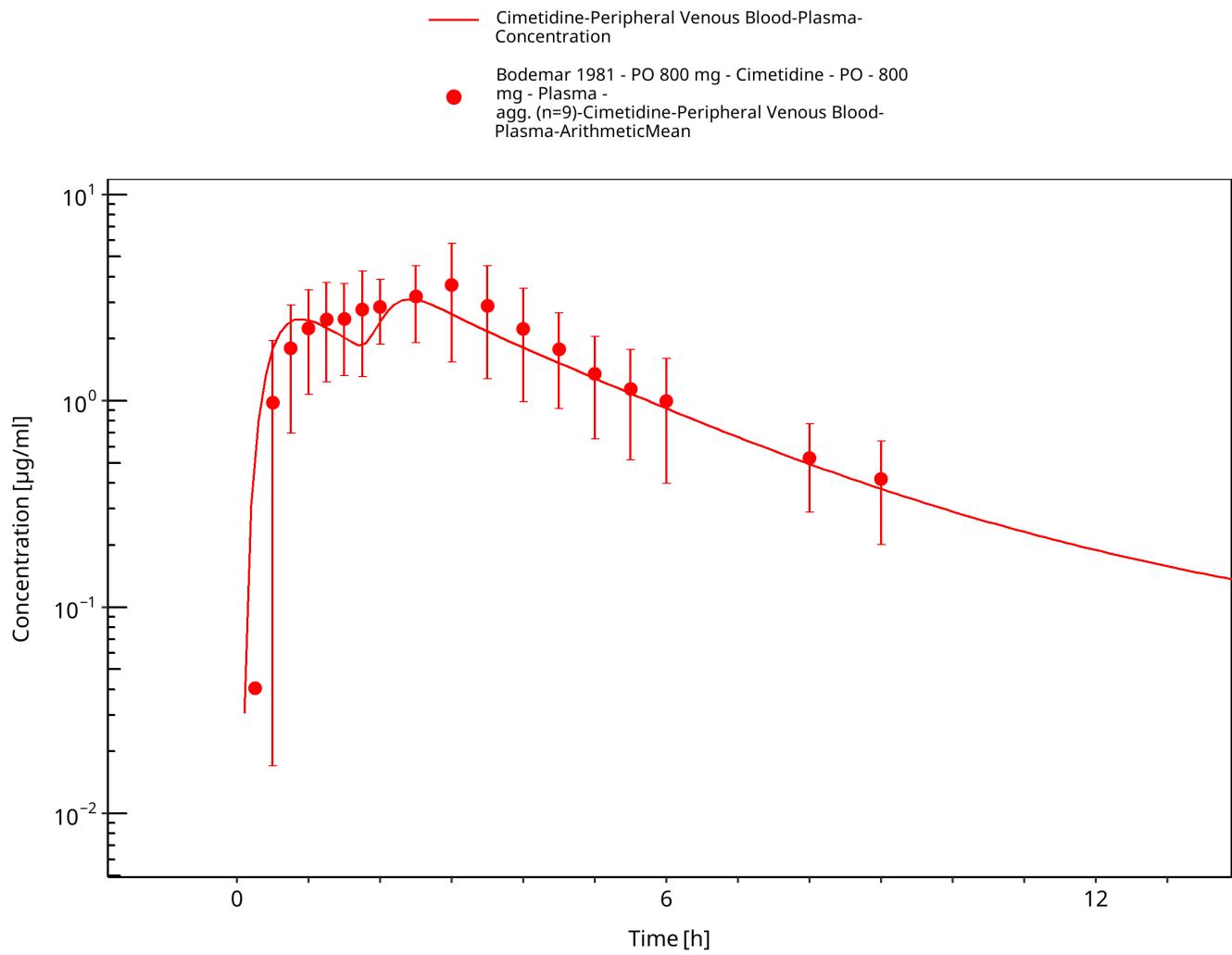


Figure 3-13: po 800 mg, Bodemar 1981, n=9

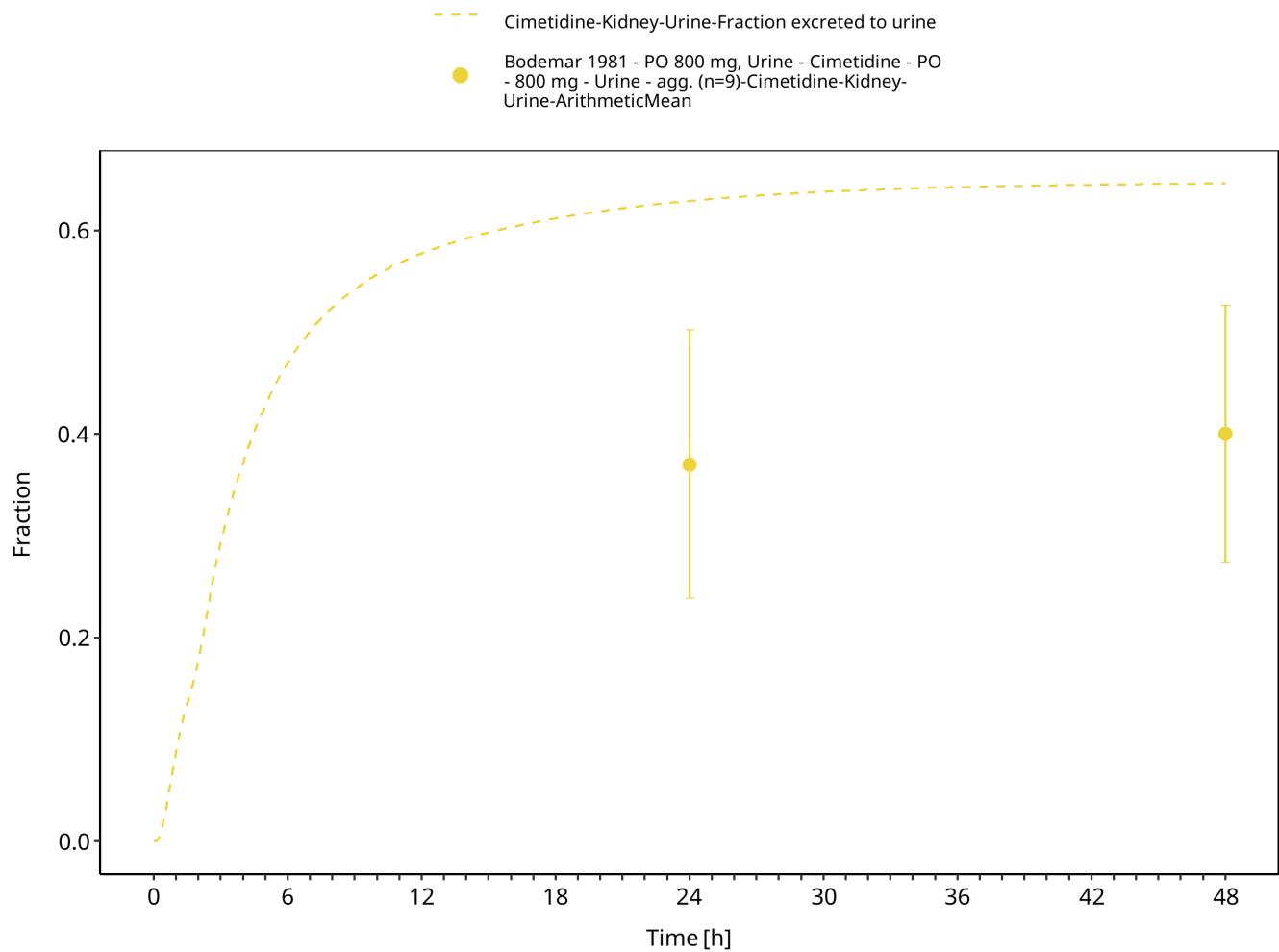


Figure 3-14: po 800 mg, Bodemar 1981, n=9, urine

3.3.2 Model Validation

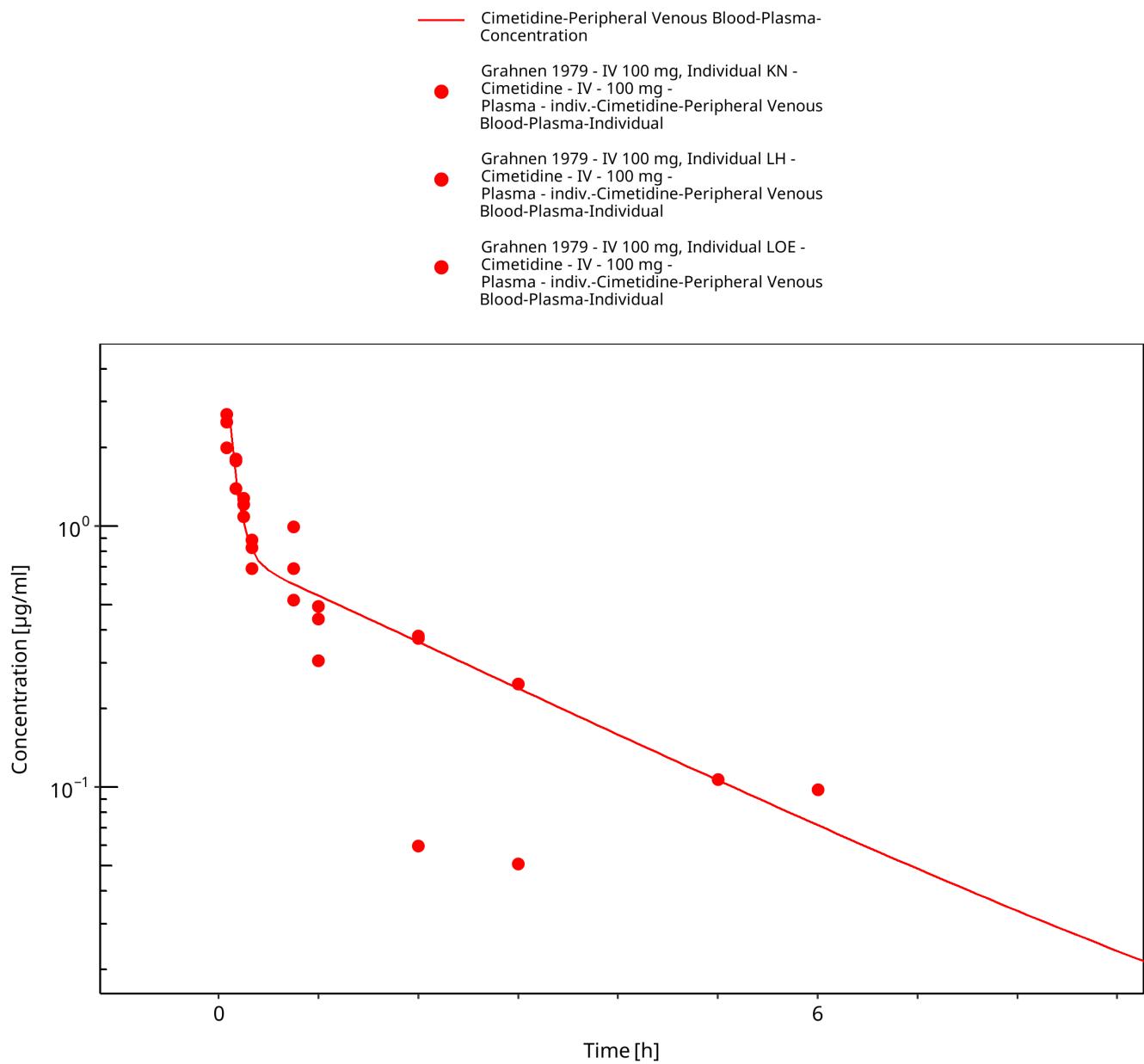


Figure 3-15: iv 100 mg (5 min), Grahnen 1979, n=3

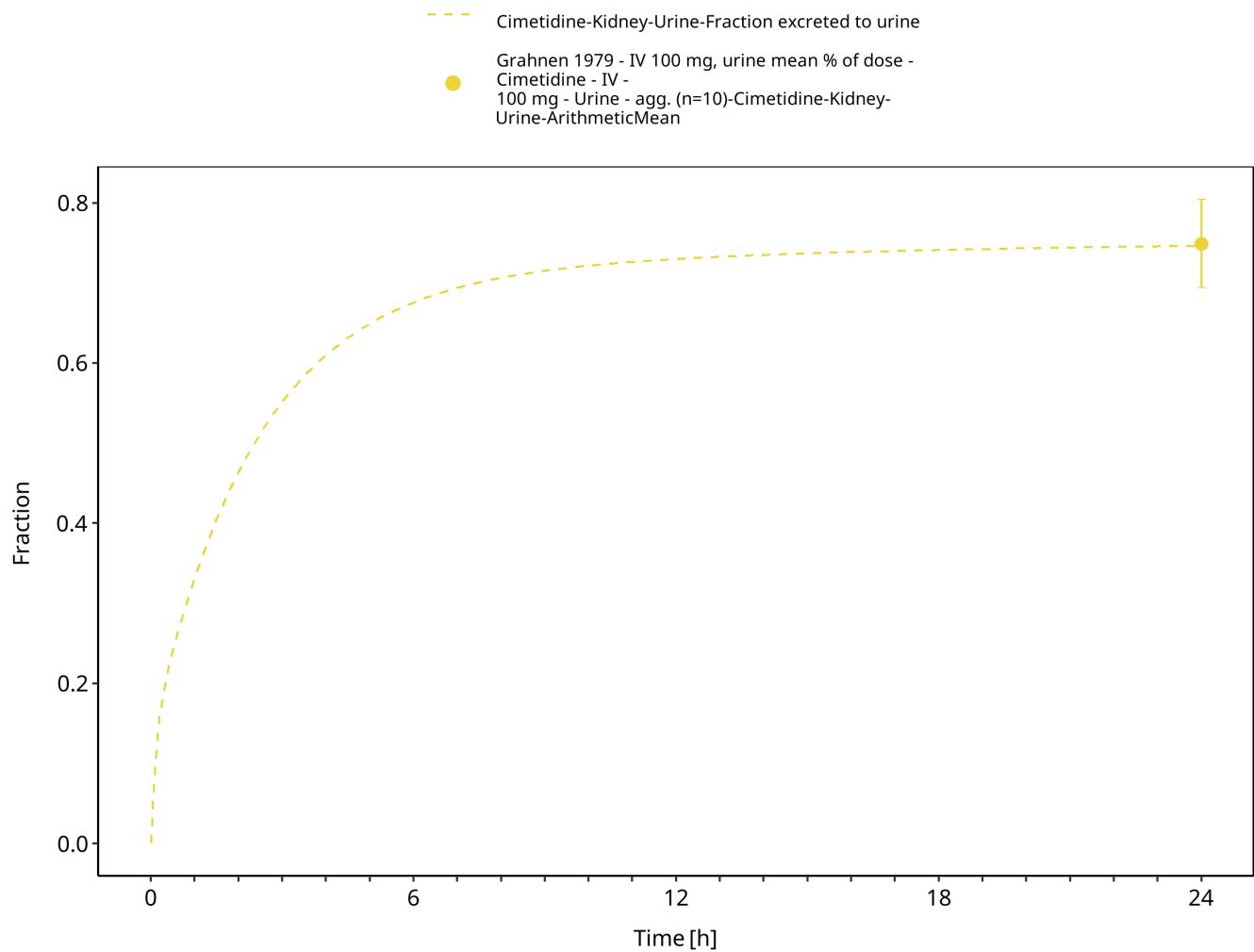


Figure 3-16: iv 100 mg (5 min), Grahnen 1979, n=3, urine

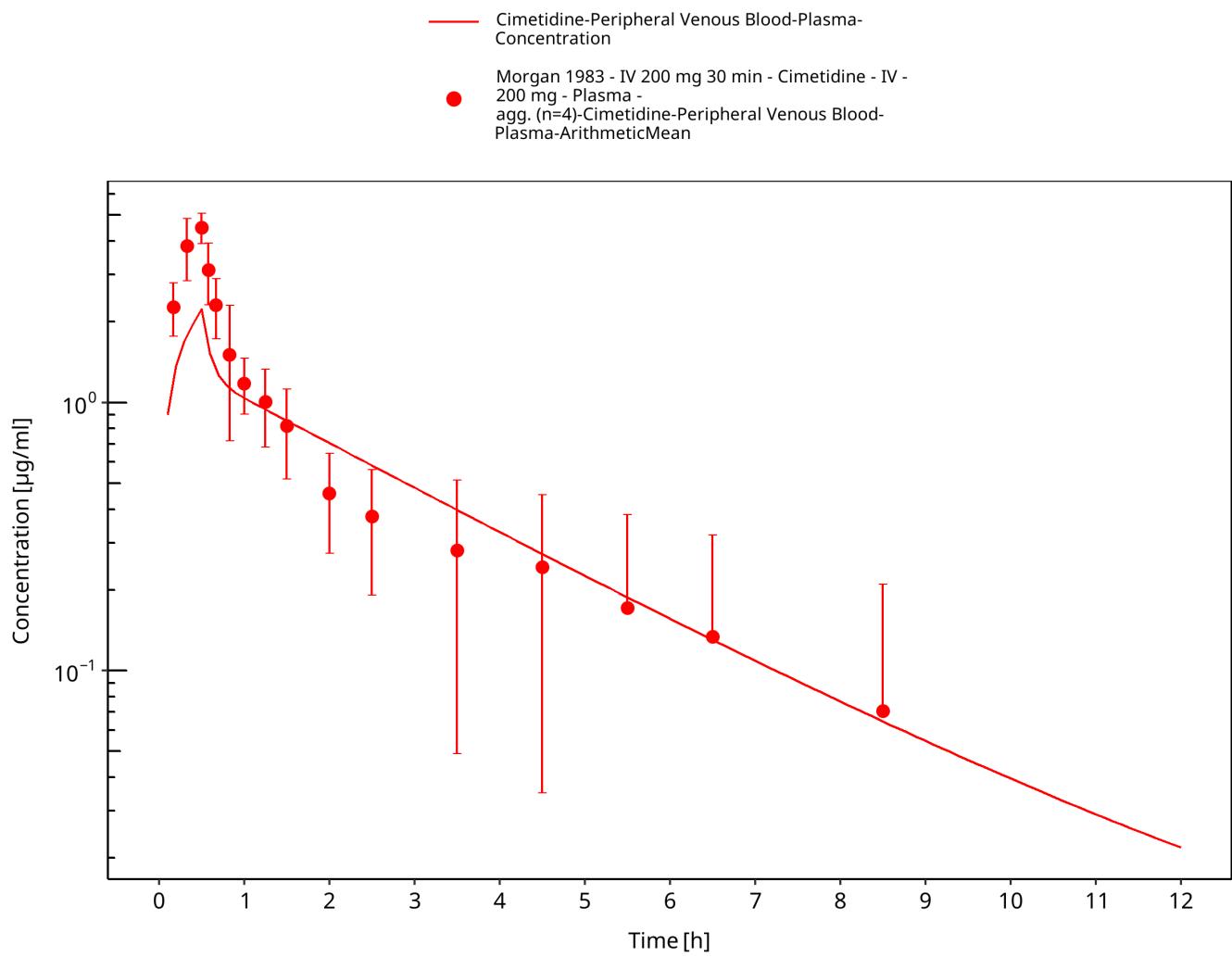


Figure 3-17: iv 200 mg (30 min),Morgan 1983, n=4

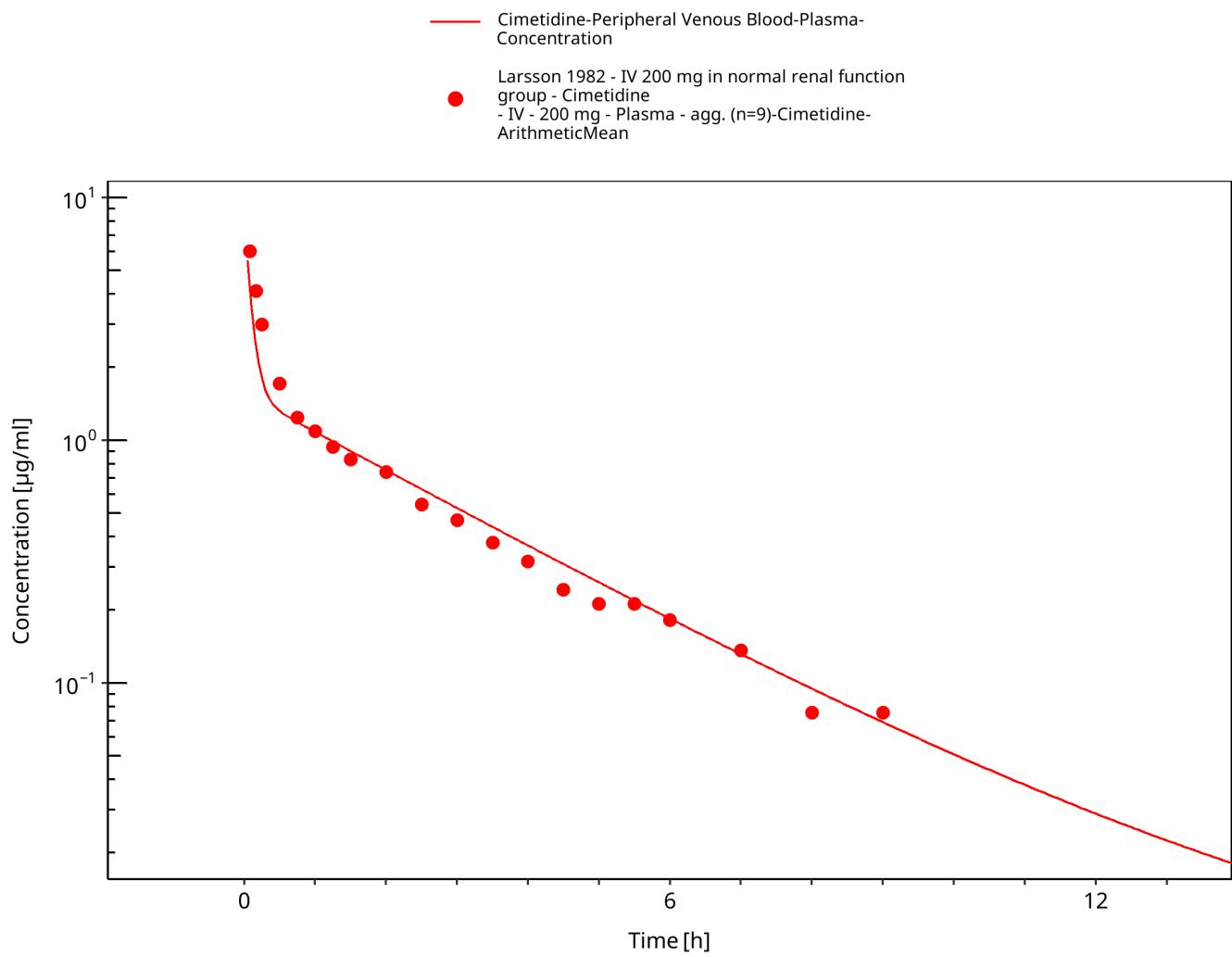


Figure 3-18: iv 200 mg, Larsson 1982, n=9

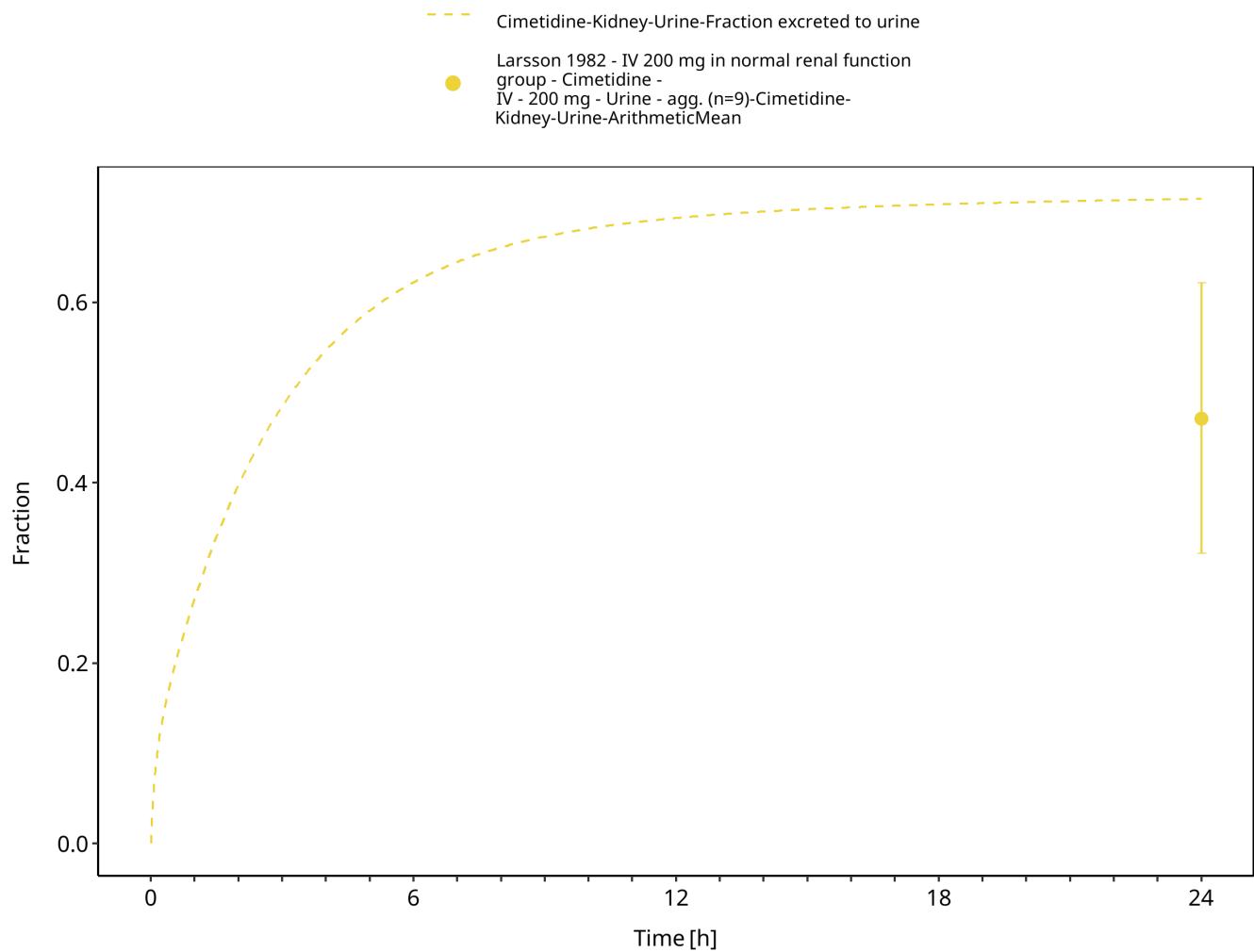


Figure 3-19: iv 200 mg, Larsson 1982, n=9, urine

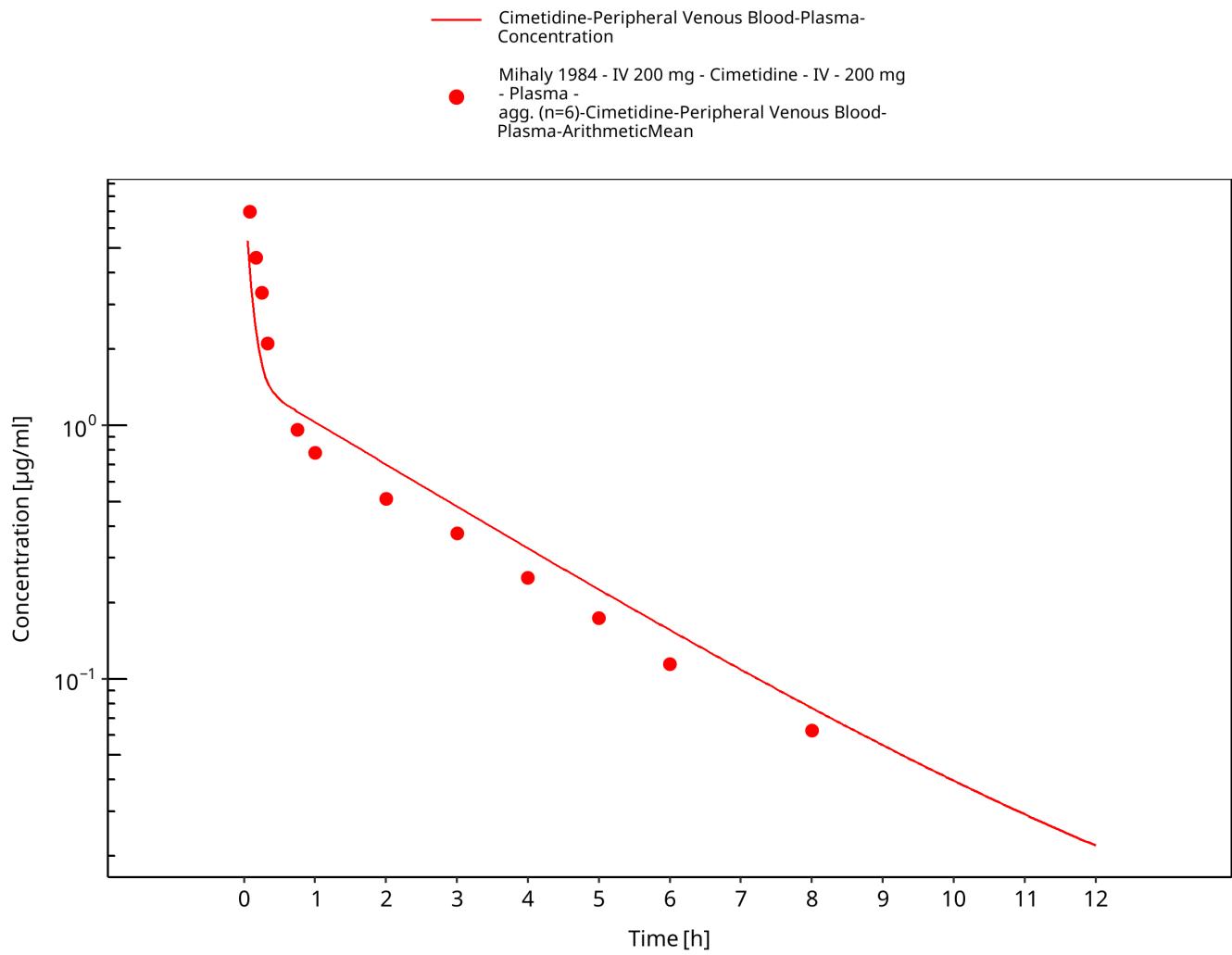


Figure 3-20: iv 200 mg, Mihaly 1984, n=6

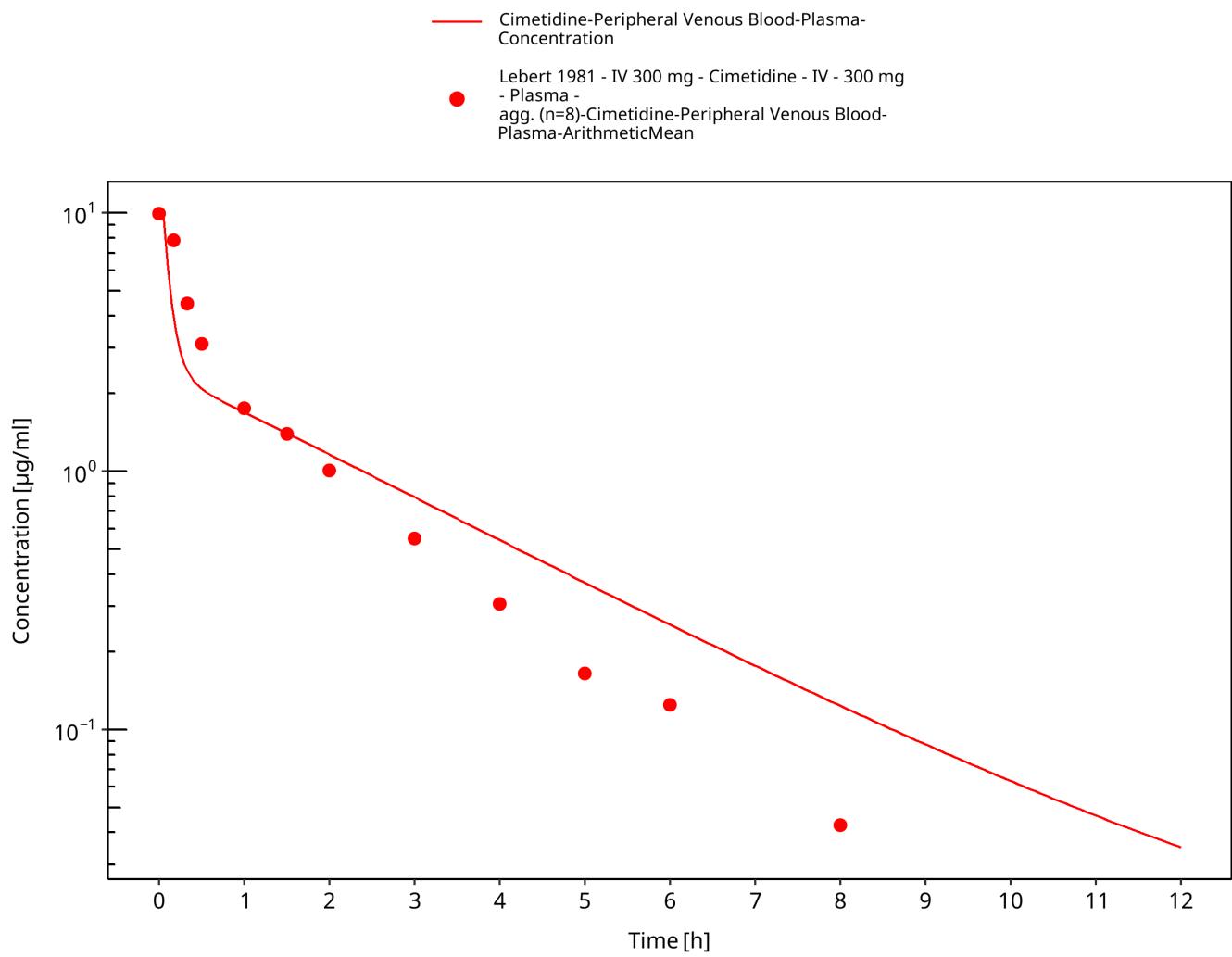


Figure 3-21: iv 300 mg (2 min), Lebert 1981, n=1

— 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.

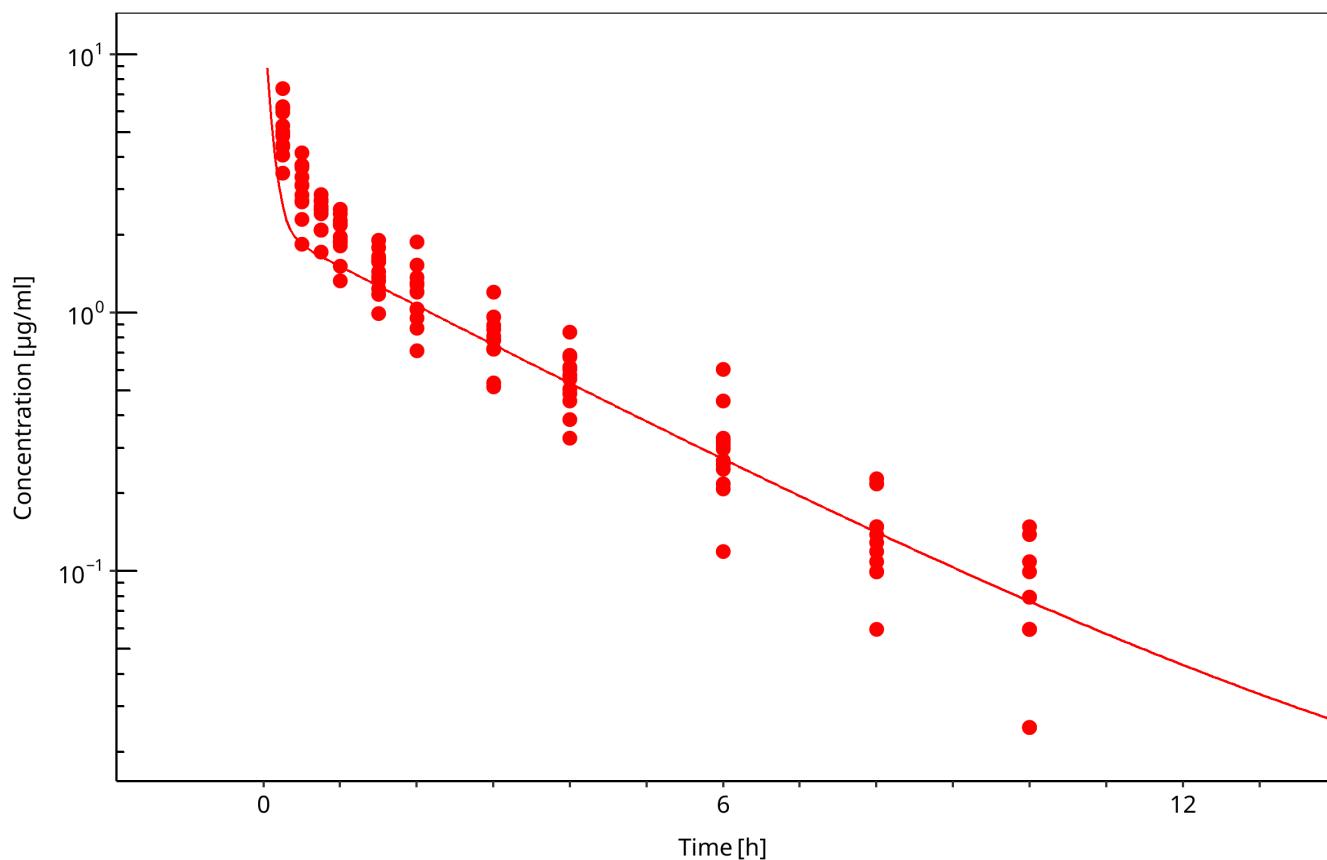


Figure 3-22: iv 300 mg (2 min), Walkenstein 1978, n=12

- 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

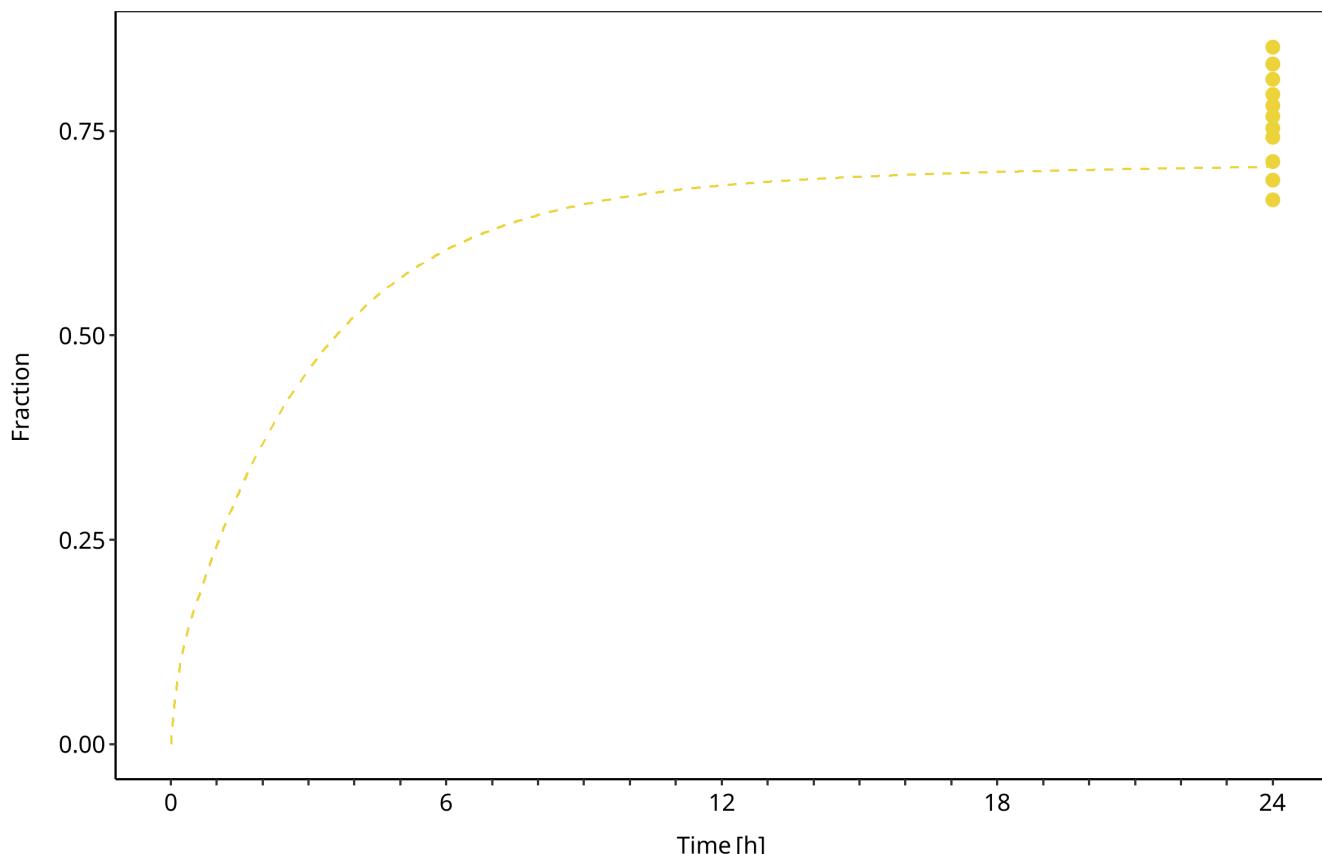


Figure 3-23: iv 300 mg (2 min), Walkenstein 1978, n=12

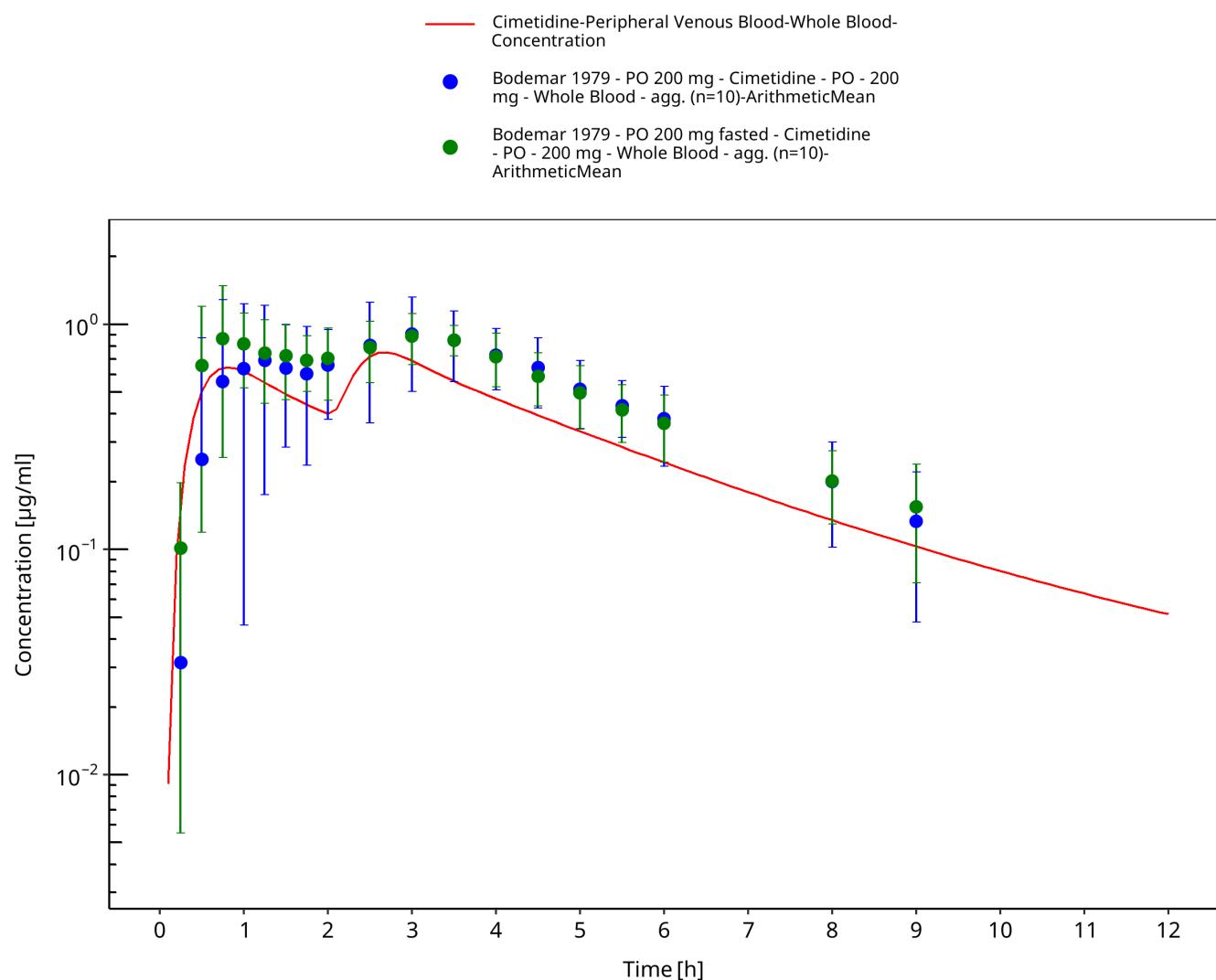


Figure 3-24: po 200 mg (tab), Bodemar 1979 (fasted)

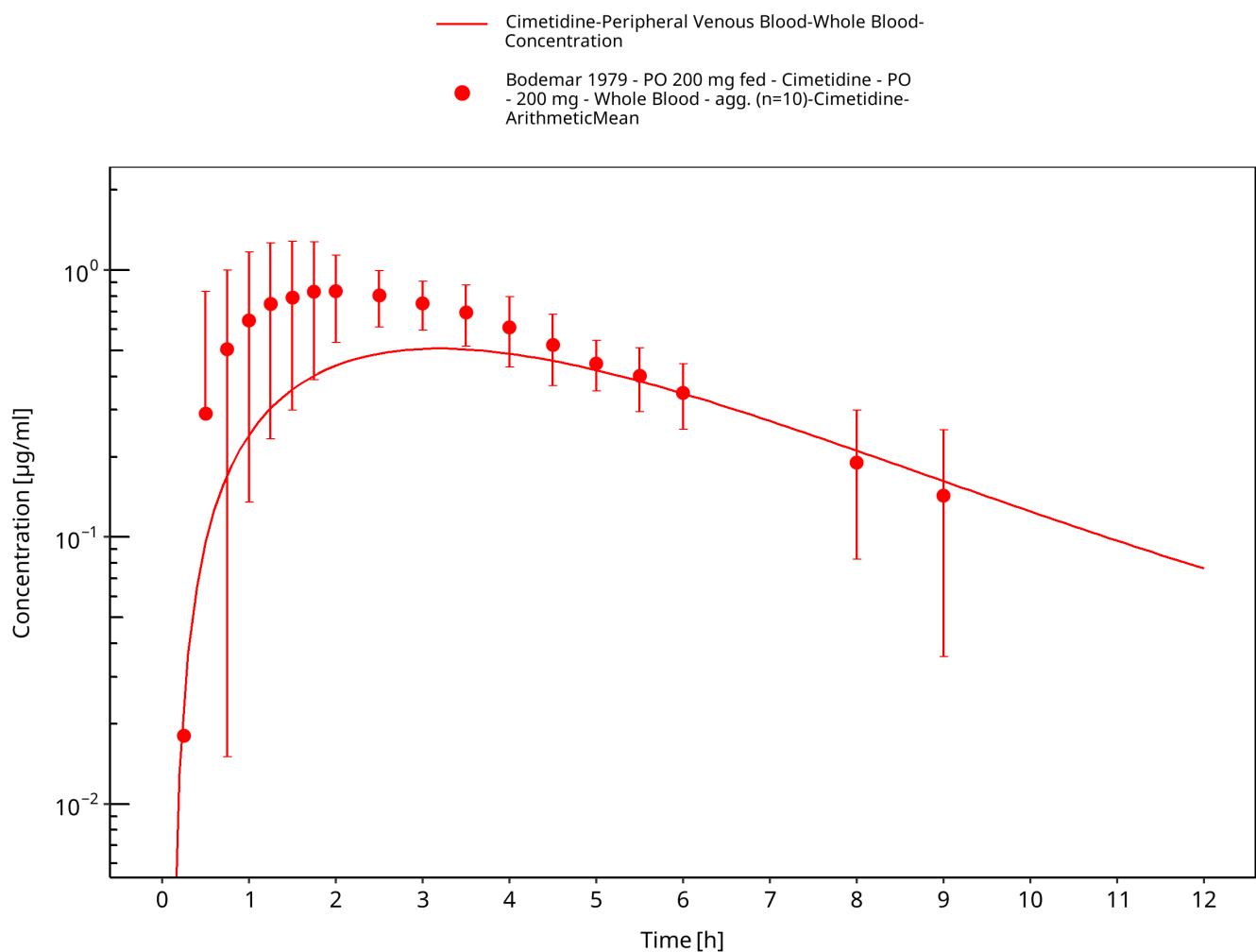


Figure 3-25: po 200 mg (tab), Bodemar 1979 (fed)

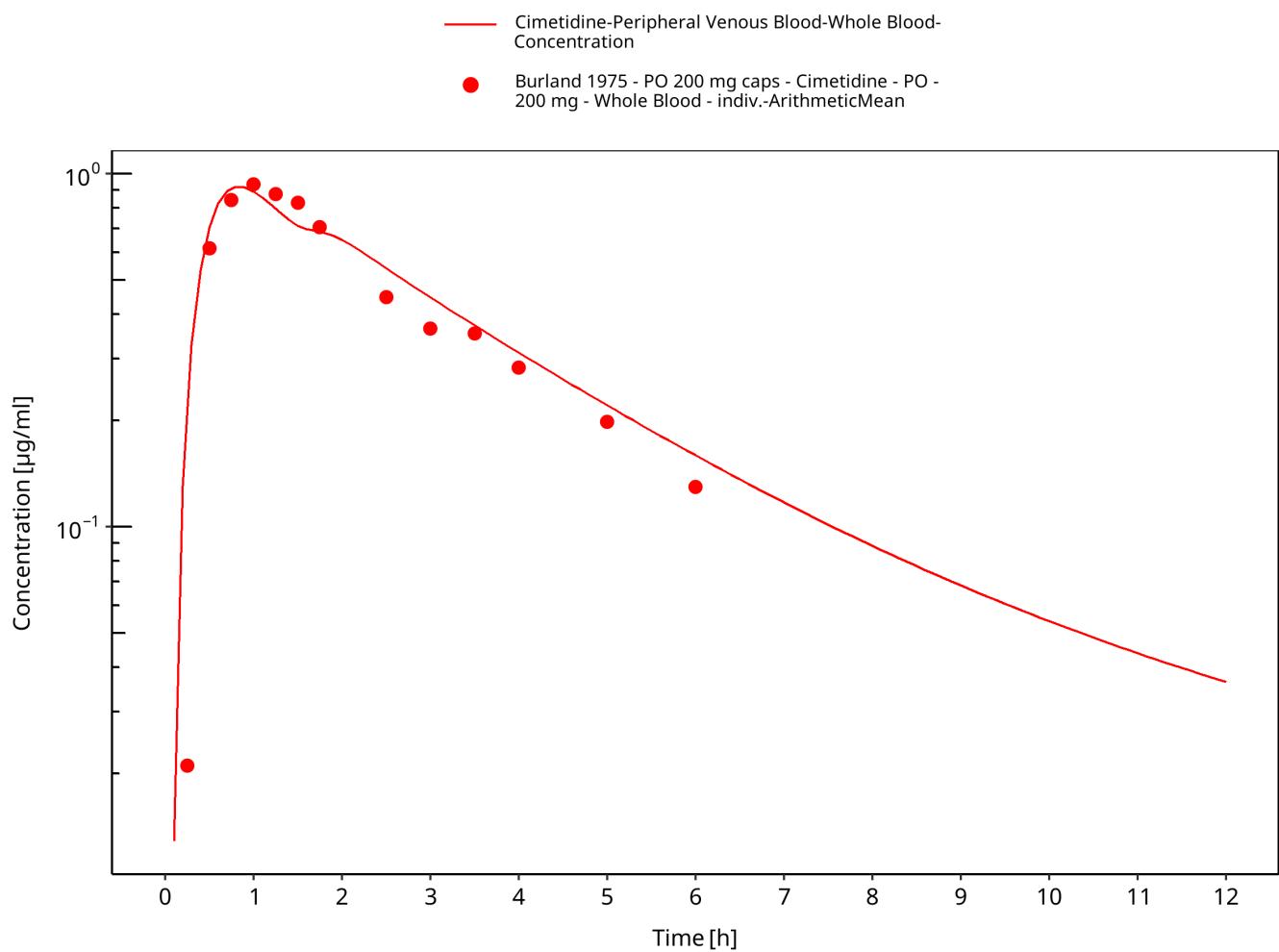


Figure 3-26: po 200 mg, Burland 1975, caps

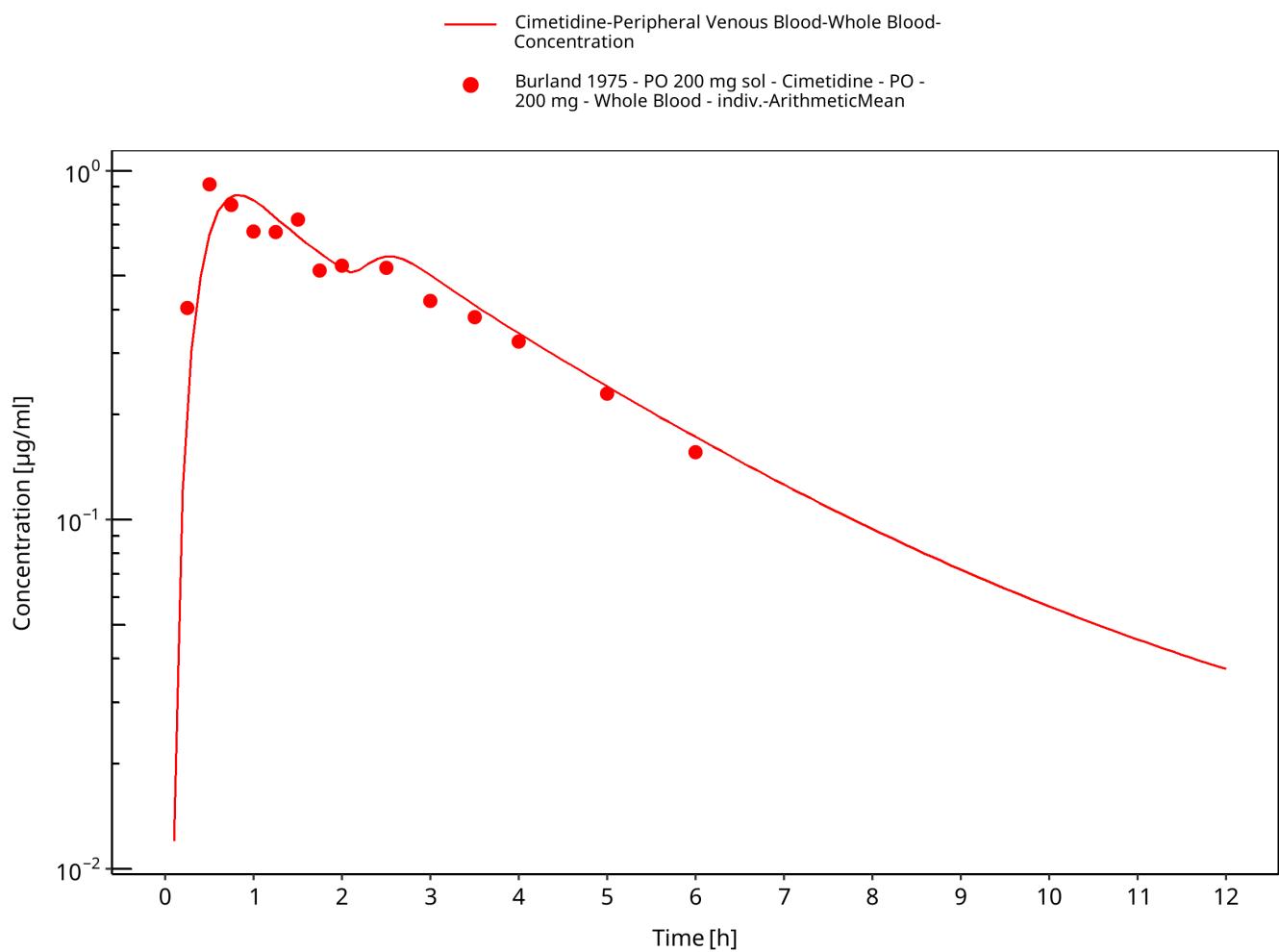


Figure 3-27: po 200 mg, Burland 1975, sol

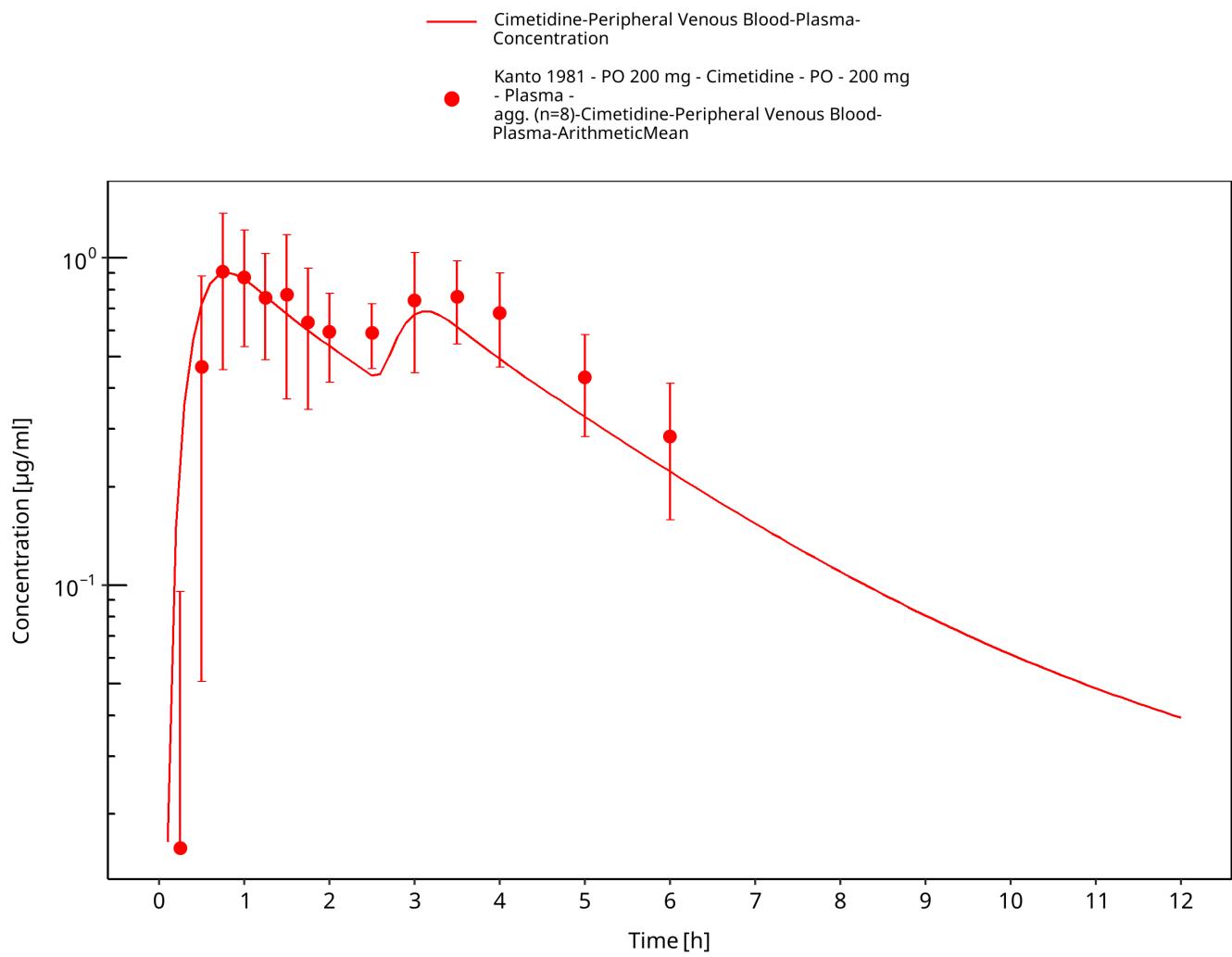


Figure 3-28: po 200 mg, Kanto 1981, n=8

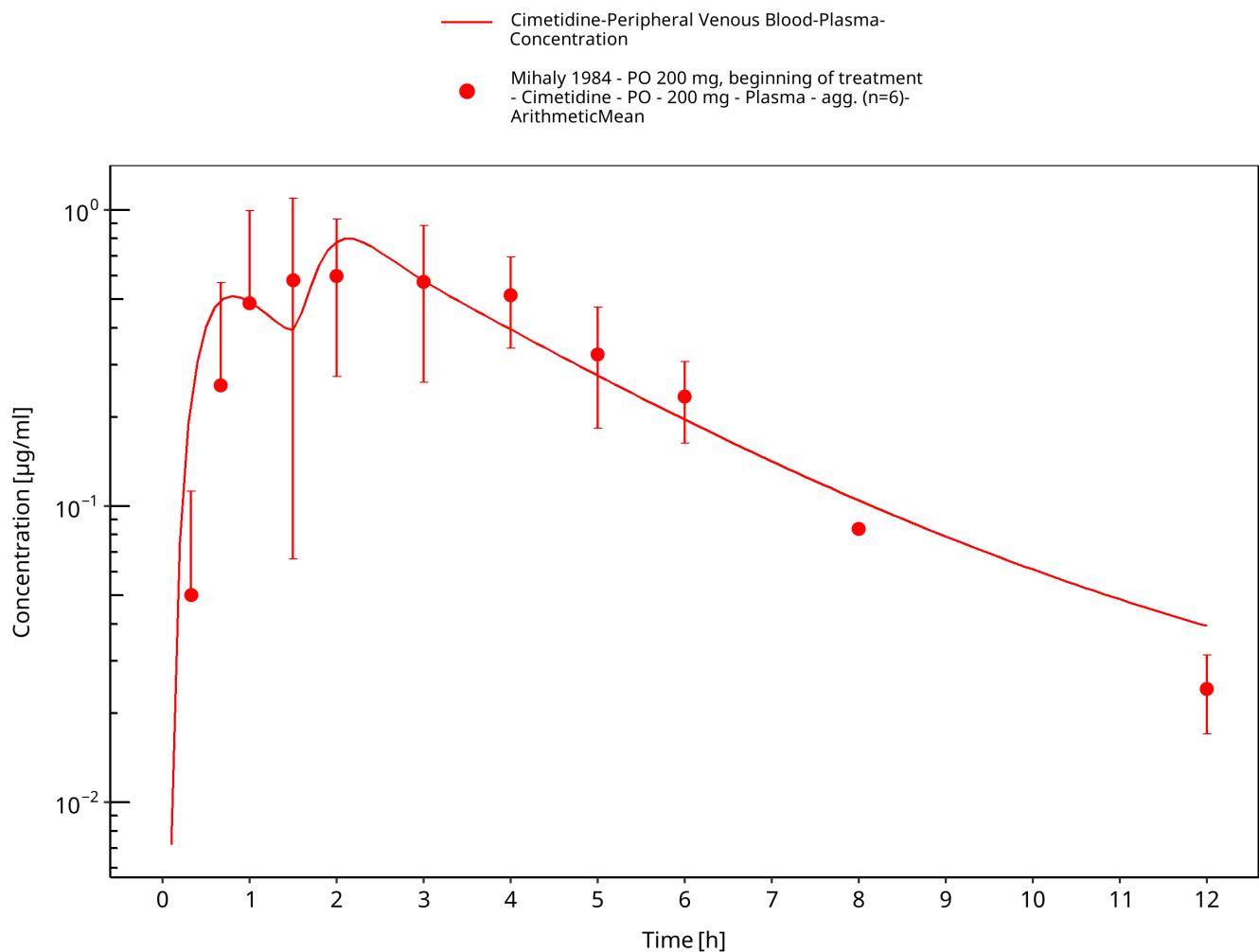


Figure 3-29: po 200 mg, Mihaly 1984, n=8

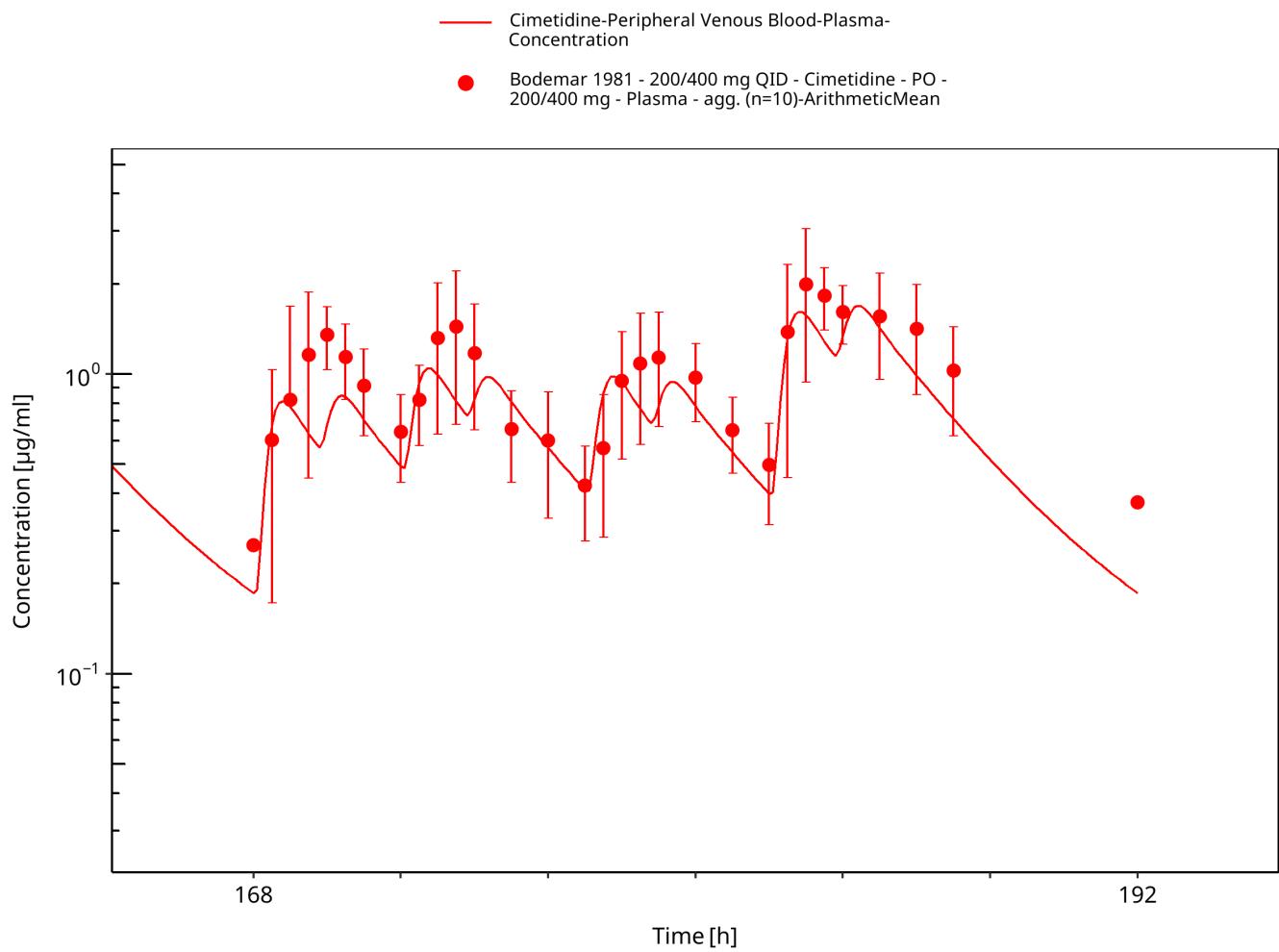


Figure 3-30: po 200/400 mg QID, Bodemar 1981 (fasted)

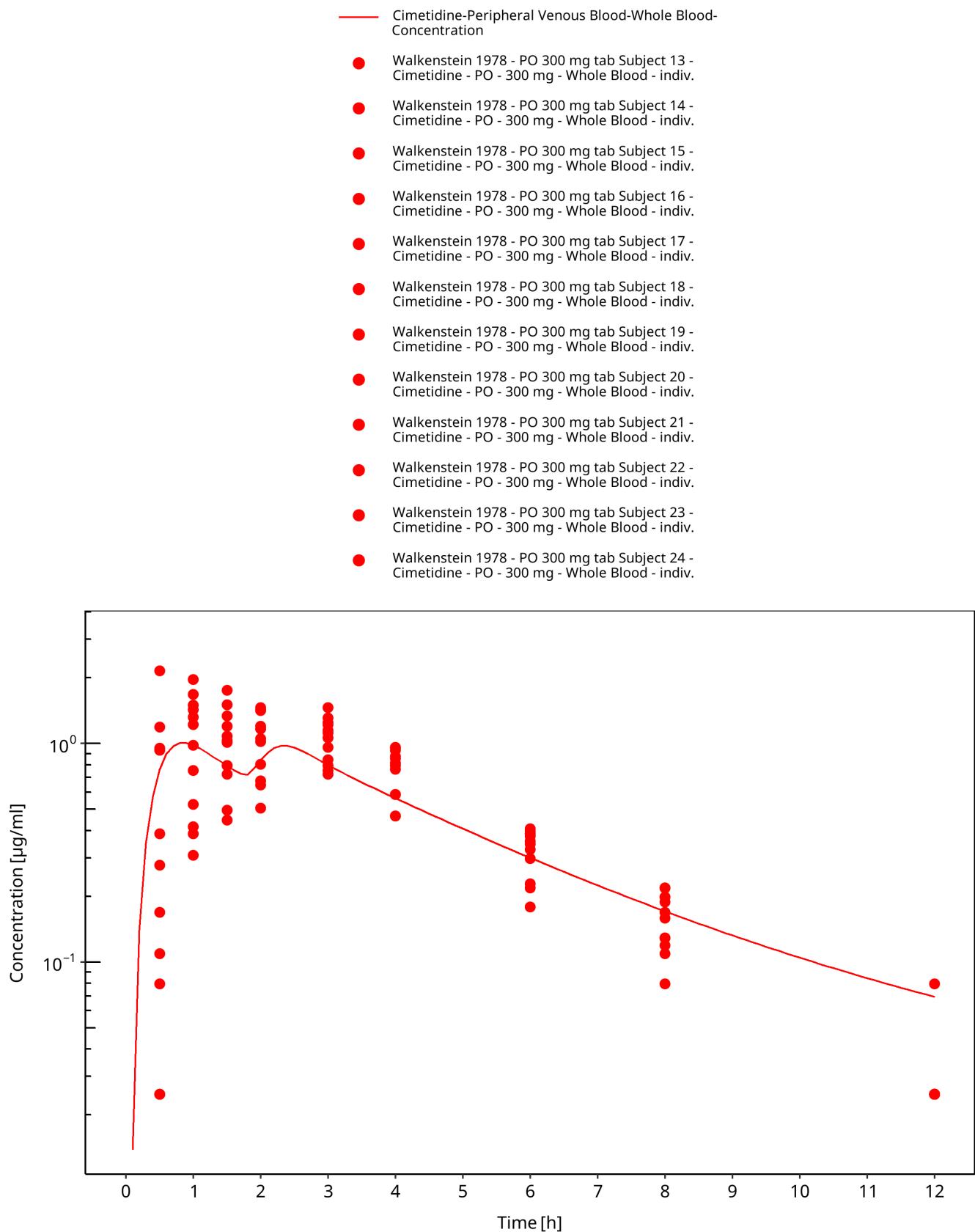


Figure 3-31: po 300 mg (tabl), Walkenstein 1978, n=12

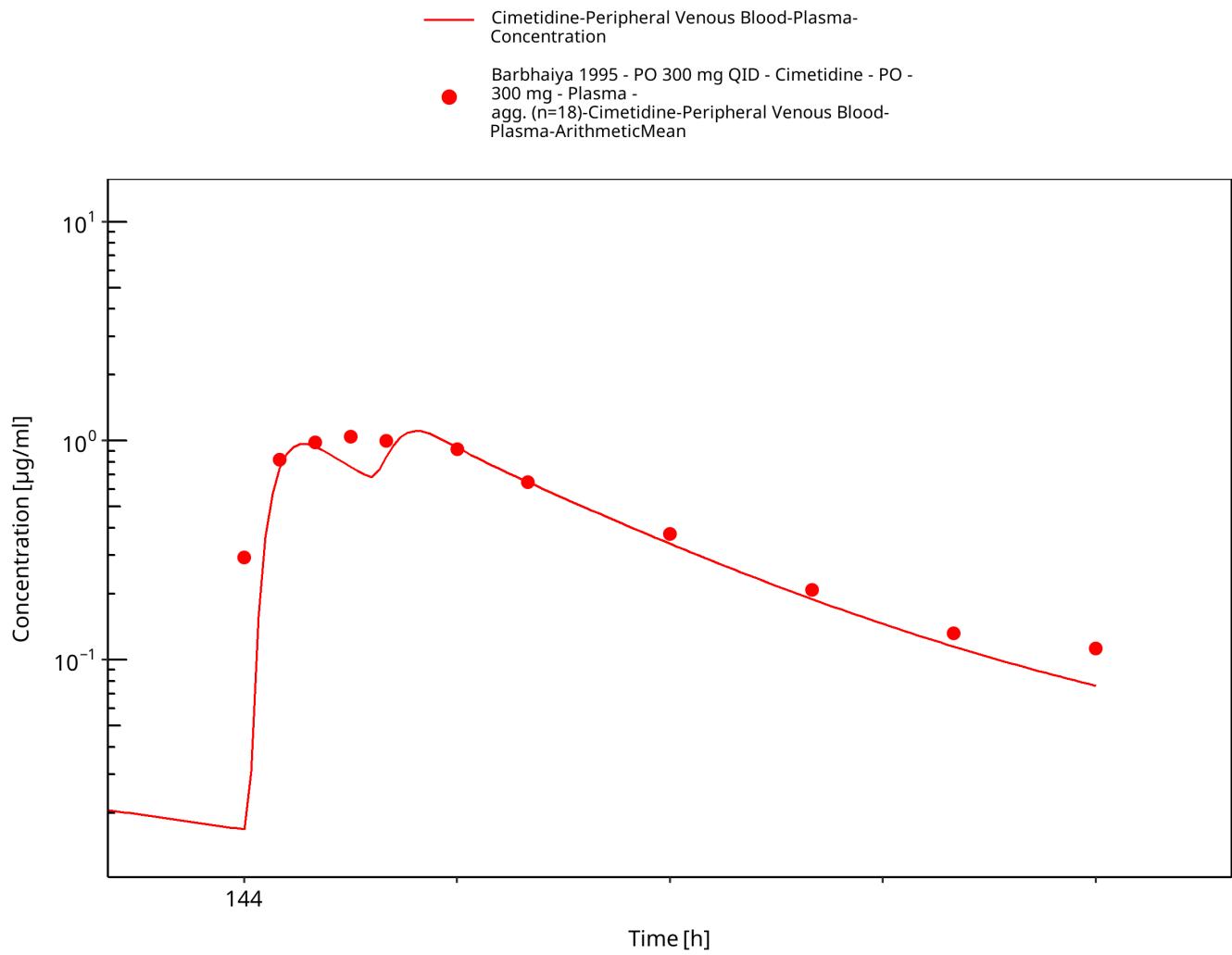


Figure 3-32: po 300 mg QID (sol), Barbhaiya 1995, n=18

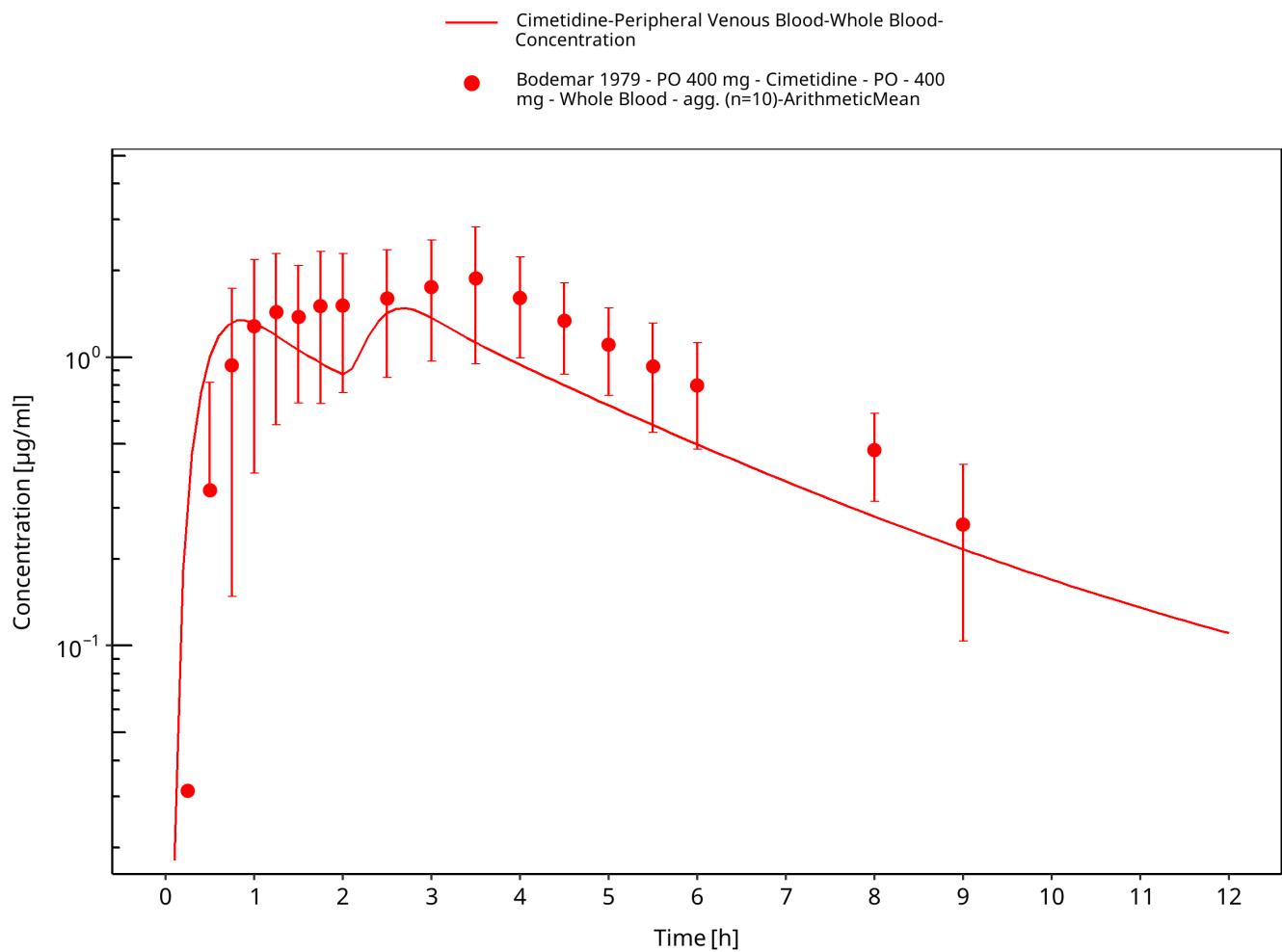


Figure 3-33: po 400 mg (tab), Bodemar 1979, n=10

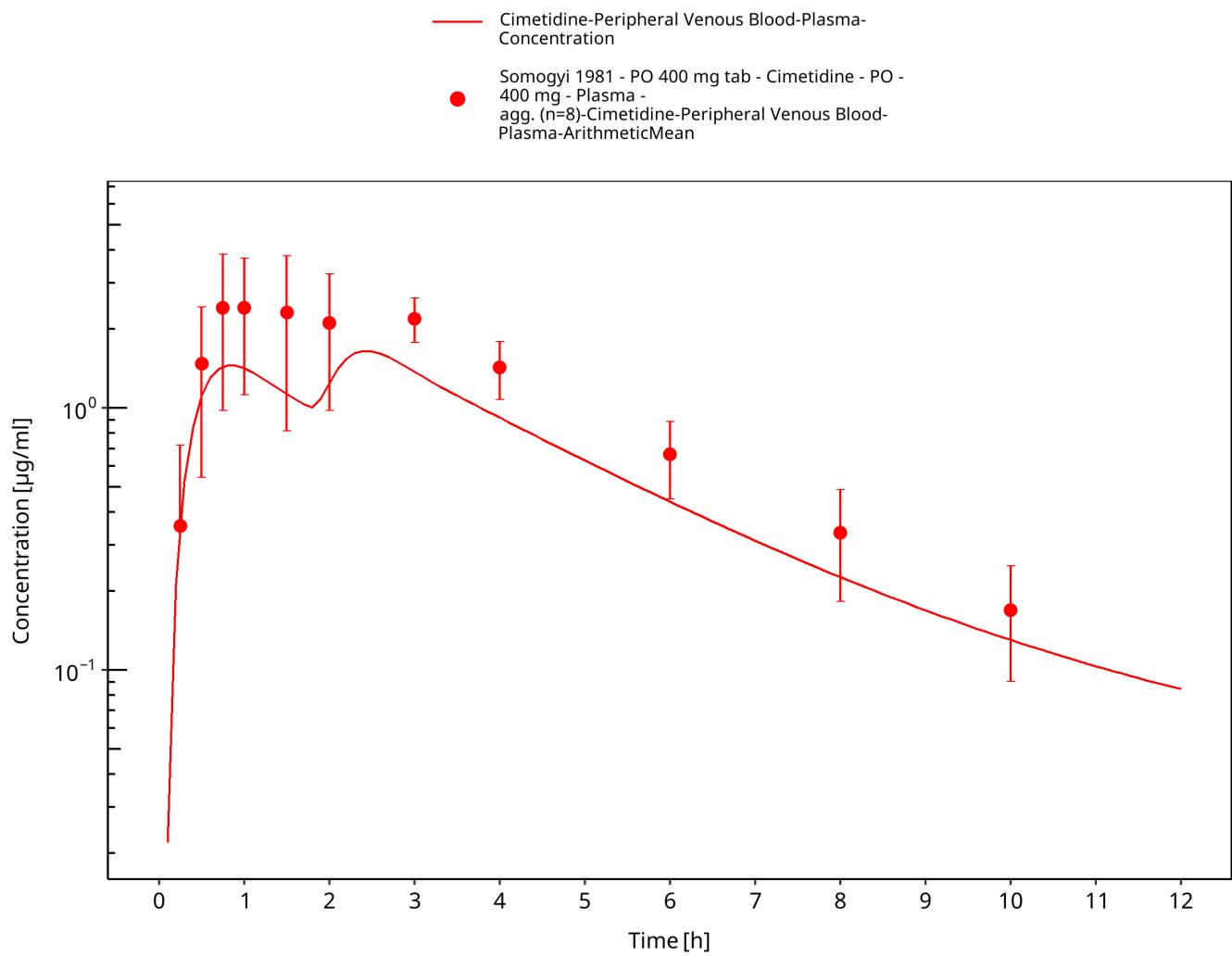


Figure 3-34: po 400 mg (tab), Somogyi 1981, n=8

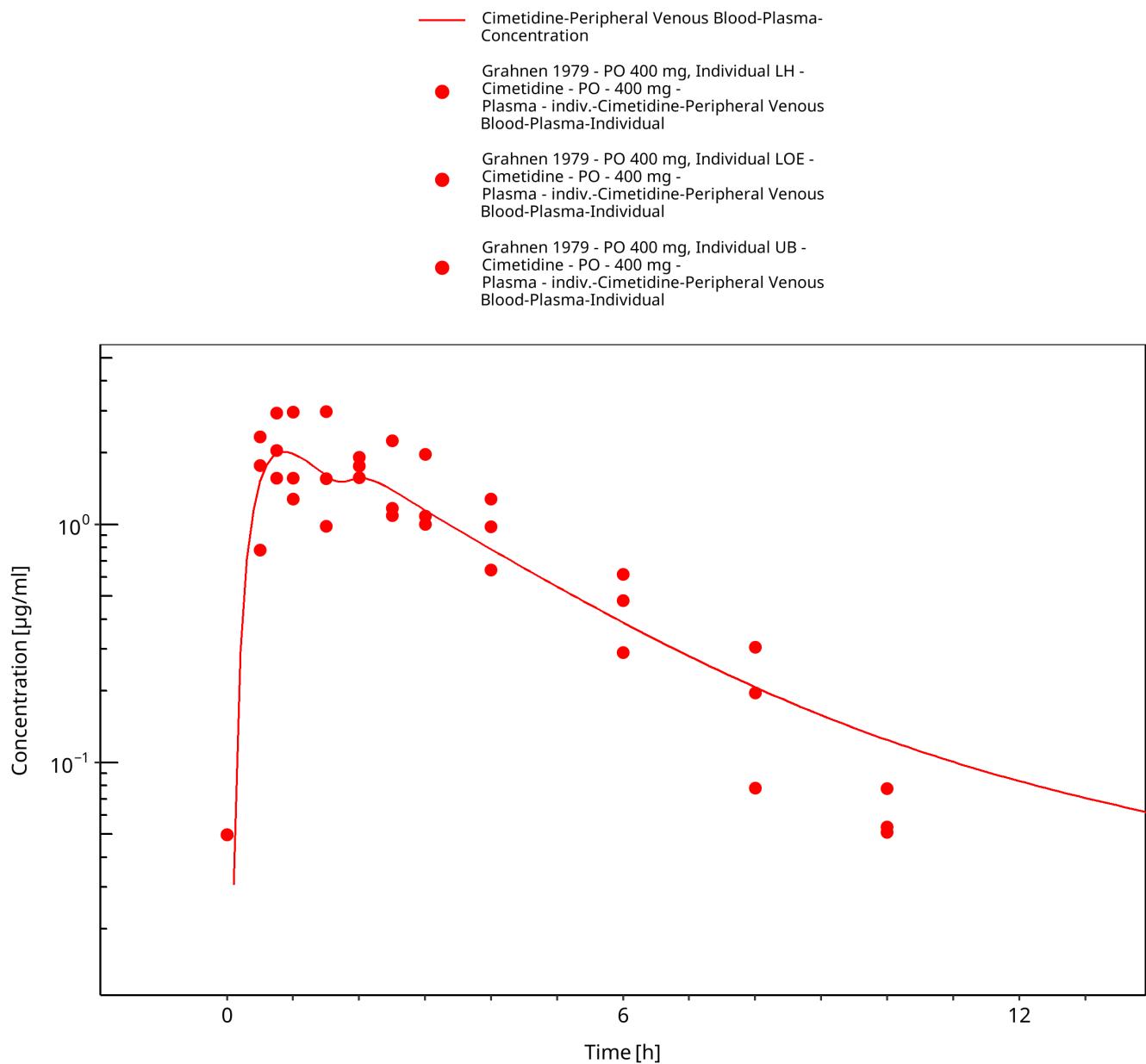


Figure 3-35: po 400 mg (tab),Grahnen 1979, n=3

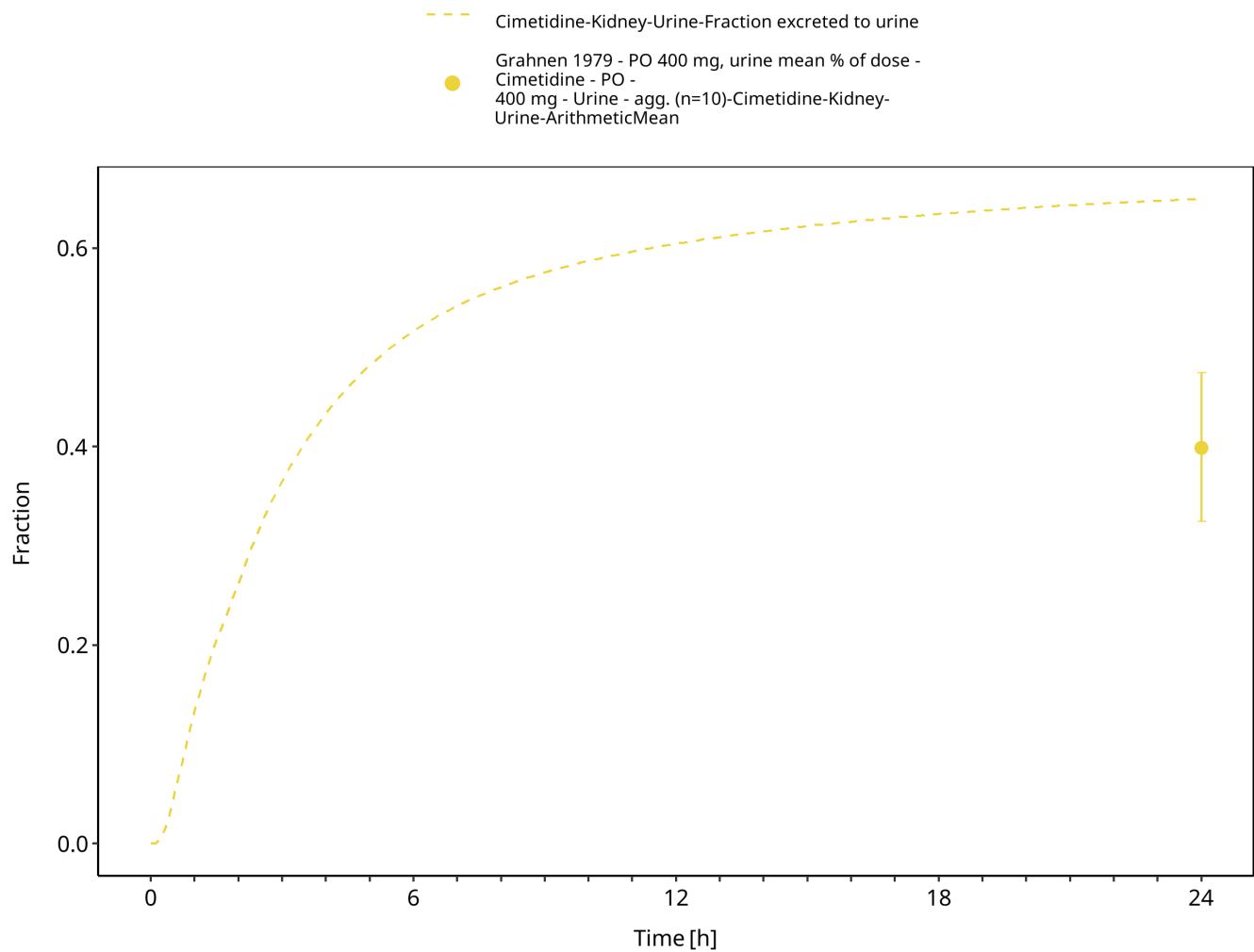


Figure 3-36: po 400 mg (tab),Grahnen 1979, n=3, urine

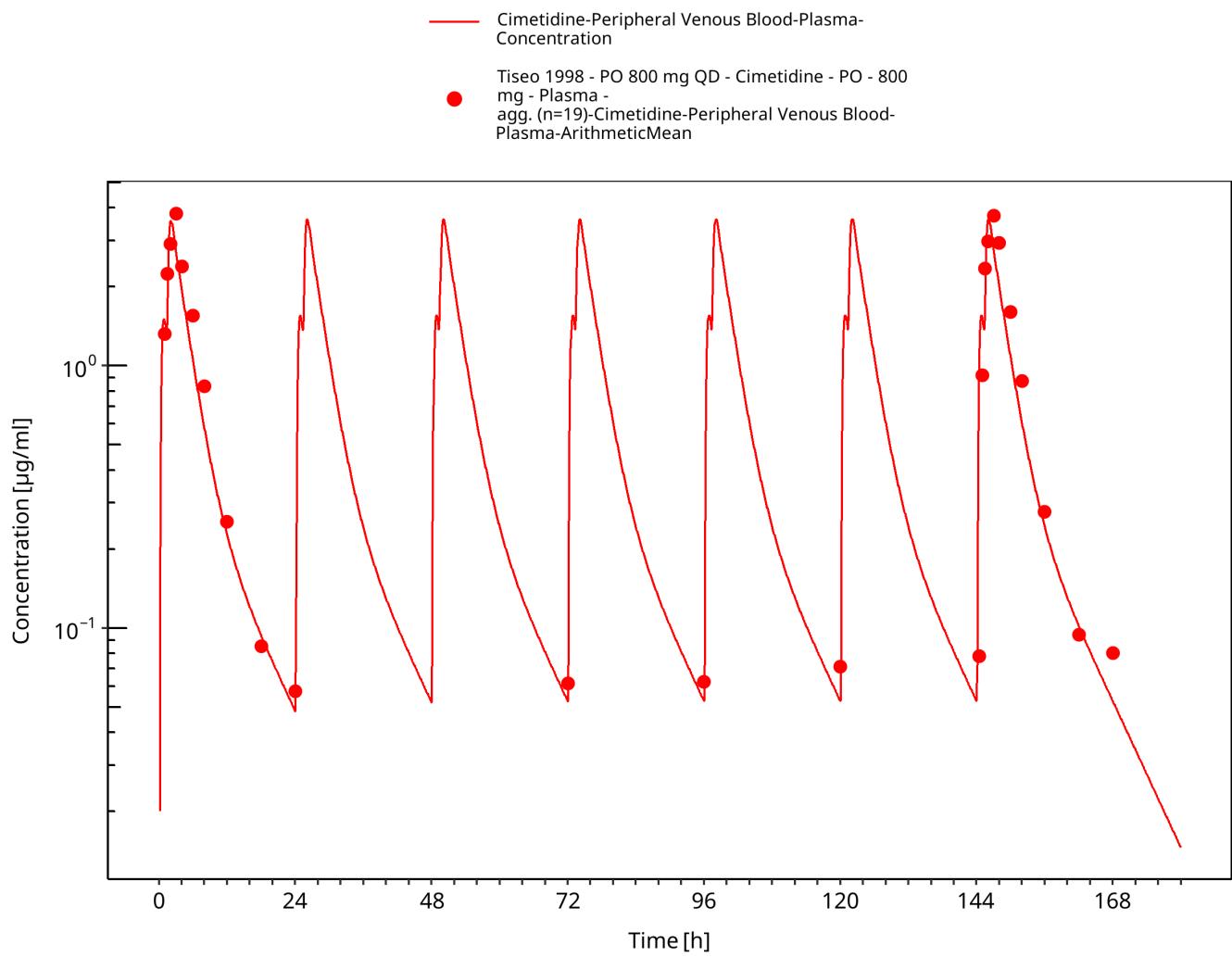


Figure 3-37: po 800 mg (tab) qd, Tiseo 1998, n=18

4 Conclusion

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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