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

Version	1.0-OSP12.1
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Probenecid-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

Probenecid is a uricosuric agent for the treatment of gout and hyperuricemia and is also used to increase plasma concentrations of antibiotics. It is metaboliszed by UGT1A9, transported by OAT3 and renally excreted by glomerular filtration and subject of tubular reabsorbtion (GFR <1). About 72% to 86% of an oral dose of probenecid is excreted in urine and of this fraction only 0.3-5% are excreted unchanged. Probenecid is an inhibitor of OAT1, OAT3, UGT1A9, MRP4 (ABCC4) and OATP1B1 and can therefore serve as a perpetrator for these transporters in DDI studies.

The herein presented PBPK model of probenecid has been developed using published pharmacokinetic clinical data by Dayton 1963 (Dayton 1963), Emanuelsson 1987 (Emanuelsson 1987), Vree 1992 (Vree 1992), Selen 1982 (Selen 1982), Wiebe 2020 (Wiebe 2020) and Landersdorfer 2009 (Landersdorfer 2009). The model has then been evaluated by comparing observed data to simulations of both intravenously and orally administered probenecid covering a dose range of 500 mg to 2000 mg. Both single dose and multiple dose administration are represented in the development and evaluation data sets.

The presented model includes the following features:

- metabolism by UGT1A9,
- transport by OAT3,
- inhibition of OAT3, MRP4 (ABCC4) and OATP1B1,
- renal clearance by glomerular filtration and tubular reabsorption modelled by GFR <1,
- oral absorption with dissolution rate assigned to the 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.

The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available PK-Sim® Ontogeny Database Version 7.3 (PK-Sim Ontogeny Database Version 7.3) or otherwise referenced for the specific process.

A mean model was built based on clinical data from studies with intravenous and oral administration of probenecid by Dayton 1963 (Dayton 1963), Emanuelsson 1987 (Emanuelsson 1987), Vree 1992 (Vree 1992), Selen 1982 (Selen 1982), Wiebe 2020 (Wiebe 2020) and Landersdorfer 2009 Landersdorfer 2009. The studies reported individual (Dayton 1963 (Dayton 1963)) or mean (Emanuelsson 1987 (Emanuelsson 1987), Vree 1992 (Vree 1992), Selen 1982 (Selen 1982), Wiebe 2020 (Wiebe 2020) and Landersdorfer 2009 (Landersdorfer 2009)) plasma concentrations of probenecid. The studies by Vree 1992 also reported individual urine fraction of unchanged probenecid. The mean PBPK model was developed using a mean individual based on the demographic data for each study and if no demographic data were provided the following values were used; male, European, 30 years of age, 73 kg body weight and 176 cm body height. The relative tissue-specific expressions of the enzyme and transporter predominantly being involved in the metabolism/transport of probenecid (UGT1A9 and OAT3) were considered (Meyer 2012). A Weibull function was fitted to describe the oral dissolution of probenecid. For the studies conducted by Vree, the tablet was broken in half and a shorter time to maximum concentration was observed and therefore a different Weibull function was fitted for these data.

A specific set of parameters (see below) was optimized to describe the disposition of probenecid using the Parameter Identification module provided in PK-Sim®. Structural model selection was mainly guided by visual inspection and total error of the resulting description of data, 95% confidence interval of the identified parameter values and biological plausibility.

The model was then verified by simulating further clinical studies reporting pharmacokinetic concentration-time profiles after intravenous and oral administration of probenecid.

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 probenecid. The obtained information from literature is summarized in the table below, and is used for model building. Final model parameters are stated in Section 3.1.

Parameter	Unit	Value	Source	Description
MW	g/mol	285.36	Wishart 2006	Molecular weight
pK$_a$ (acid)		3.01	Avdeef 2001	acid dissociation constant of conjugate acid
		3.7	Avdeef 2003	acid dissociation constant of conjugate acid
Solubility (HIF)	mg/mL	0.74	Söderlind 2010	Aqueous Solubility in human intestinal fluid
logP		-0.52	Dayton 1963	Partition coefficient between octanol and water
		-0.23	Avdeef 2001	Partition coefficient between octanol and water
		0.13	Avdeef 2003	Partition coefficient between octanol and water
		3.21	Hansch 1995	Partition coefficient between octanol and water
		3.7	Hansch 1995	Partition coefficient between octanol and water
fu	%	6.2	Vree 1992	Fraction unbound in plasma
	%	7.56	Vree 1993	Fraction unbound in plasma
	%	11.7	Shen 2019	Fraction unbound in plasma
K$_m$ UGT1A9	µmol/L	198.3	Ito 2014	UGT1A9 Michaelis-Menten constant
Ki UGT1A9	µmol/L	242	Measured	Inhibition of UGT1A9
Ki OAT3	µmol/L	5.41	Tsuruya 2016	Inhibition of OAT3
Ki OATP1B1	µmol/L	39.8	Izumi 2016	Inhibition of OATP1B1
Ki OATP1B1	µmol/L	17.89	In vivo Ki estimated based on CP-I data	Inhibition of OATP1B1
Ki MRP4 (ABCC4)	µmol/L	87.40	Probenecid-Furosemid-DDI*	Inhibition of MRP4

*To describe the competitive inhibition of MRP4 by probenecid, the corresponding inhibition constant was optimized during the furosemide PBPK model parameter identification, using the clinical data of one of the probenecid-furosemide interaction studies (Probenecid-Furosemid-DDI Repository).

2.2.2 Clinical data

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

The following publications were found in adults for model building:

Publication	Arm / Treatment / Information used for model building
Dayton 1963	Individual plasma PK profiles in healthy subjects after single intravenous administration of 464.20 and 1860 mg probenecid
Emanuelsson 1987	Plasma PK profiles in healthy subjects after single intravenous infusion (15 min) of 500 mg probenecid and single oral administration of 2000 mg probenecid
Vree 1992	Plasma PK profiles and urine data in healthy subjects after single oral administration of 250 and 1500 mg probenecid
Selen 1992	Plasma PK profiles in healthy subjects after single oral administration of 500, 1000 and 2000mg probenecid
Wiebe 2020	Plasma PK profiles in healthy subjects after multiple oral administration of 1000 mg probenecid
Landersdorfer 2009	Plasma PK profiles in healthy subjects after multiple oral administration of 250, 500 and 1000 mg probenecid

The following table shows the data from the excretion studies (Vree 1992) used for model building:

Observer	Value
Fraction excreted to urine of unchanged probenecid after oral administration 1000 mg	2%
Fraction excreted to urine of unchanged probenecid after oral administration 1500 mg	5%
Fraction excreted to urine of unchanged probenecid after oral administration 500 mg	0.3%
Fraction excreted to urine of unchanged probenecid after oral administration 250 mg	1.1%

The following dosing scenarios were simulated and compared to respective data for model verification:

Scenario	Data reference
iv bolus 464.2 mg	Dayton 1963
iv bolus 1860 mg	Dayton 1963
po 500 mg	Emanuelsson 1987 and Vree 1992
po 1000 mg	Emanuelsson 1987, Shen 2019, Vree 1992, Vree 1993
po 2000 mg	Dayton 1963
po 1000 mg bid for 1 day	Smith 1980
po 500 mg at 0, 1000 mg at 8 h and 500 mg at 14.5, 20.5 and 26.5 h	Landersdorfer 2010

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 results of optimization in Section 2.3.4. The measured solubility in human intestinal fluid (HIF) was used in the model (see Section 2.2.1)

The dissolution of tablets was implemented via empirical Weibull dissolution. A different Weibull function was used for the studies by Vree (Vree 1992), as the tablets were broken in half and an shorter time to reach maximum concentration was observed, see results of optimization in Section 2.3.4.

2.3.2 Distribution

Probenecid is highly bound to plasma proteins (approx. 88 %) (see Section 2.2.1). A value of 12% 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 values are in the range of -0.52 to 3.7 (see Section 2.2.1) which served as a starting value. Finally, the model parameter `Lipophilicity` was optimized to match clinical data (see also Section 2.3.4).

After testing the available organ-plasma partition coefficient and cell permeability calculation methods built in PK-Sim, observed clinical data was best described by choosing the partition coefficient calculation by `PK-Sim Standard` and cellular permeability calculation by `Charge dependent Schmitt normalized to PK-Sim`.

2.3.3 Metabolism and Elimination

One metabolic pathway was implement into the model via Michaelis-Menten kinetics

- UGT1A9

The UGT1A9 expression profiles is based on high-sensitive real-time RT-PCR (Nishimura 2003). Metabolic enzyme activity was described as saturable process following Michaelis-Menten kinetics, were the `Km` was taken from literature measured in liver microsomes and the `kcat` was optimized based on clinical data (see Section 2.3.4).

And one transport protein was implemented into the model via Michaelis-Menten kinetics

- OAT3

The OAT3 expression profiles is based on high-sensitive real-time RT-PCR (Nishimura 2003). Transporter activity was described as saturable process following Michaelis-Menten kinetics, were both `Km` and `kcat` was optimized based on clinical data (see Section 2.3.4).

Additionally, renal clearance assumed to be mainly driven by glomerular filtration and tubular reabsorption modelled as GFR <1 was implemented. The `GFR fraction` was identified to best describe the observed fraction of unchanged probenecid that was renally excreted (see Section 2.3.4).

2.3.4 Automated Parameter Identification

These are the parameters estimated in the final parameter identification:

Model Parameter
`Lipophilicity`
`GFR fraction`
`kcat` (UGT1A9)
`km` (OAT3)
`kcat` (OAT3)
`Specific intestinal permeability`
`Dissolution time (50% dissolved)`
`Dissolution shape`
`Dissolution time (50% dissolved)` (Broken tablet)
`Dissolution shape` (broken tablet)

3 Results and Discussion

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

The model was built and evaluated covering data from studies including in particular

- single intravenous administration and both single and multiple oral administrations (tablets).
- a dose range of 250 to 2000 mg.

The model quantifies excretion via urine (glomerular filtration and reabsorption assigned to reduced GFR), metabolism via UGT1A9 and transport by OAT3.

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 Probenecid final input parameters

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

Compound: Probenecid

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	738 mg/l	Publication-In Vitro-Söderlind 2010, HIF	Söderlind 2010, HIF	True
Reference pH	7	Publication-In Vitro-Söderlind 2010, HIF	Söderlind 2010, HIF	True
Lipophilicity	1.3396899029 Log Units	Parameter Identification-Parameter Identification-Value updated from 'IV_PO_TAB_GFRfraction_without Land 2010_250919_LM_FINAL2' on 2019-12-18 15:32	Avdeef 2003	True
Fraction unbound (plasma, reference value)	0.117	Publication-In Vitro-Vree 1992	Vree 1992	True
Specific intestinal permeability (transcellular)	0.0003971252633 cm/min	Parameter Identification-Parameter Identification-Value updated from 'IV_PO_TAB_GFRfraction_without Land 2010_250919_LM_FINAL2' on 2019-12-18 15:32	fitted	True
Is small molecule	Yes			
Molecular weight	285.359 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	0.0298169506	Parameter Identification-Parameter Identification-Value updated from 'IV_PO_TAB_GFRfraction_without Land 2010_250919_LM_FINAL2' on 2019-12-18 15:32

Inhibition: OAT3-Tsuruya 2016

Molecule: OAT3

Parameters

Name	Value	Value Origin
Ki	5.41 µmol/l	Publication-In Vitro-Tsuruya 2016

Metabolizing Enzyme: UGT1A9-Ito 2014

Molecule: UGT1A9

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	59 pmol/min/mg mic. protein	Publication-In Vitro-Ito 2014
Km	198.3 µmol/l	Publication-In Vitro-Ito 2014
kcat	74.9179385436 1/min	Parameter Identification-Parameter Identification-Value updated from 'IV_PO_TAB_GFRfraction_without Land 2010_250919_LM_FINAL2' on 2019-12-18 15:32

Transport Protein: OAT3-assumed

Molecule: OAT3

Parameters

Name	Value	Value Origin
Transporter concentration	1 µmol/l	
Vmax	0 µmol/l/min	
Km	12.1775959667 µmol/l	Parameter Identification-Parameter Identification-Value updated from 'IV_PO_TAB_GFRfraction_without Land 2010_250919_LM_FINAL2' on 2019-12-18 15:32
kcat	1118.97811 1/min	Other-Manual Fit-obtained by optimited Kcat value in V9 * 0.569. 0.569 is the ratio of OAT3 amount in V9/V11 with script transporterFactorsOAT3

Inhibition: OATP1B1-Izumi 2016

Molecule: OATP1B1

Parameters

Name	Value	Value Origin
Ki	39.8 µmol/l	Publication-In Vitro-Izumi 2016

Inhibition: OATP1B1-In vivo Ki based on CP-I

Molecule: OATP1B1

Parameters

Name	Value	Value Origin
Ki	17.89 µmol/l	Parameter Identification-Parameter Identification-based on CP-I plasma levels

Inhibition: UGT1A9-Wang 2020

Molecule: UGT1A9

Parameters

Name	Value	Value Origin
Ki	242 µmol/l	Publication-In Vitro-Wang 2020

Inhibition: ABCC4-Fitted

Molecule: ABCC4

Parameters

Name	Value	Value Origin
Ki	87.396448408 µmol/l	Publication-Parameter Identification-Wiebe 2020

3.2 Probenecid 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
Probenecid iv (model building)	1.27
Probenecid oral administration (model building)	1.30
Probenecid oral administration (model verification)	1.38
All	1.33
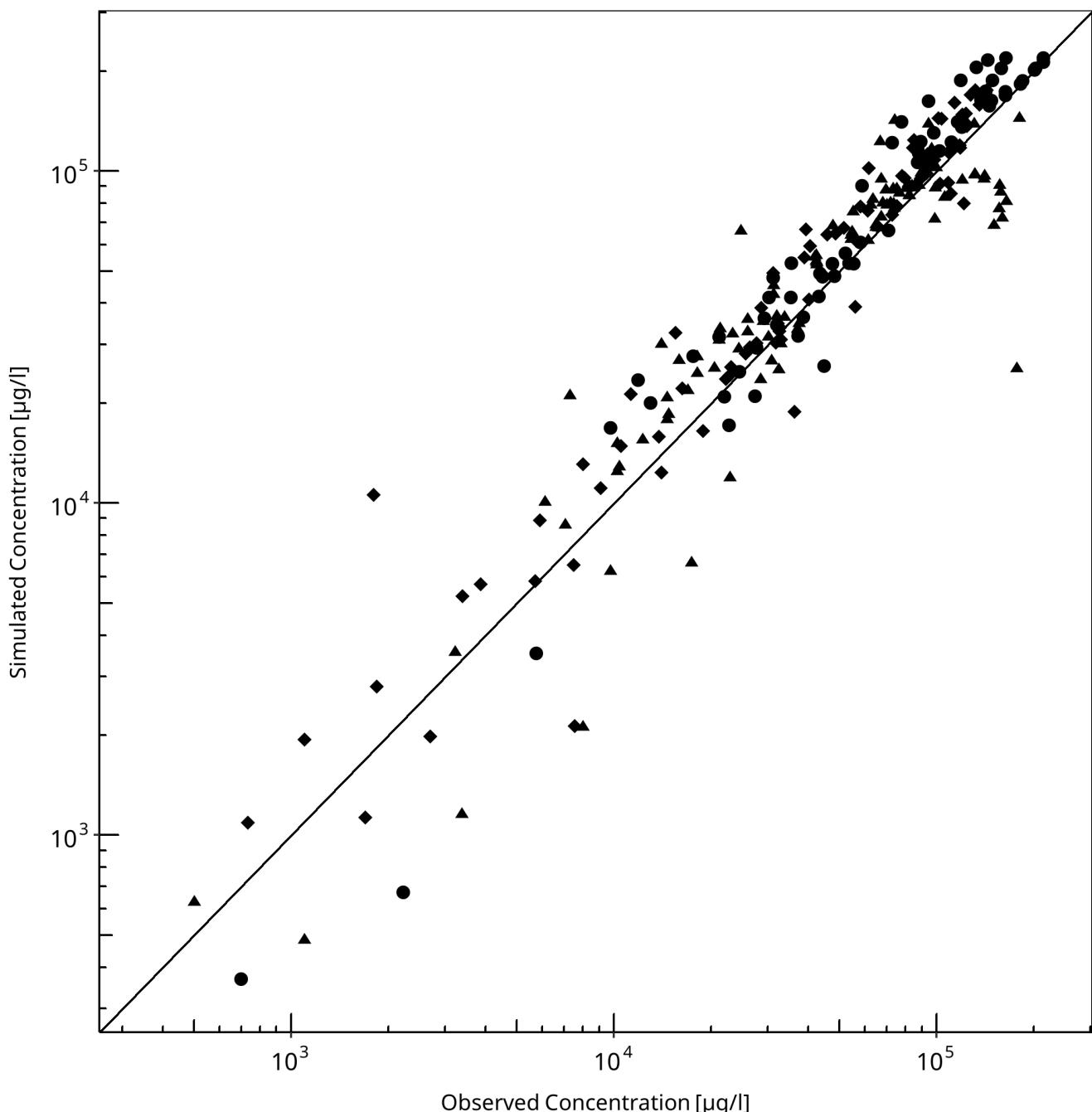
Figure 3-1: Goodness of fit plot for concentration in plasma.
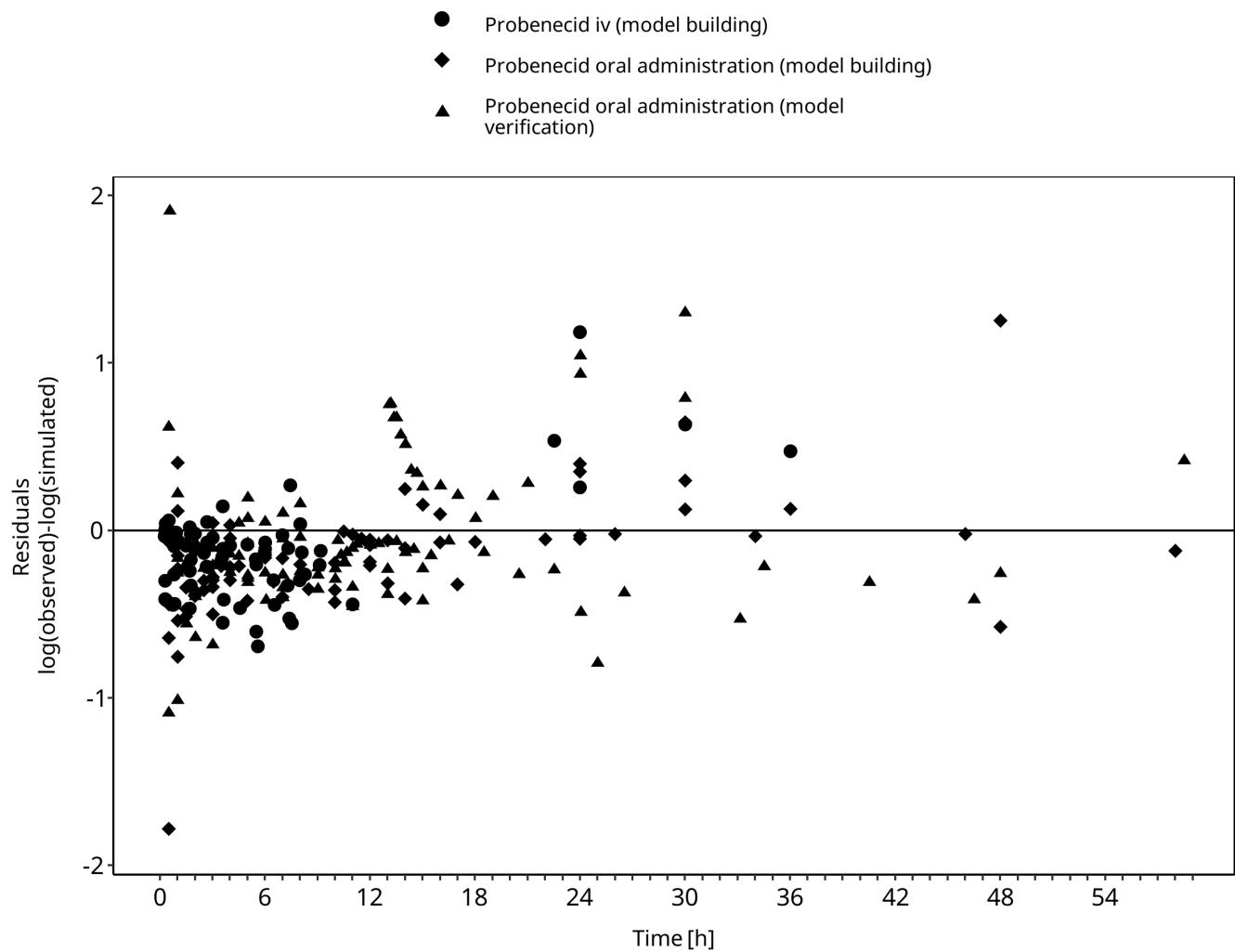
Figure 3-2: Goodness of fit plot for concentration in plasma.

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
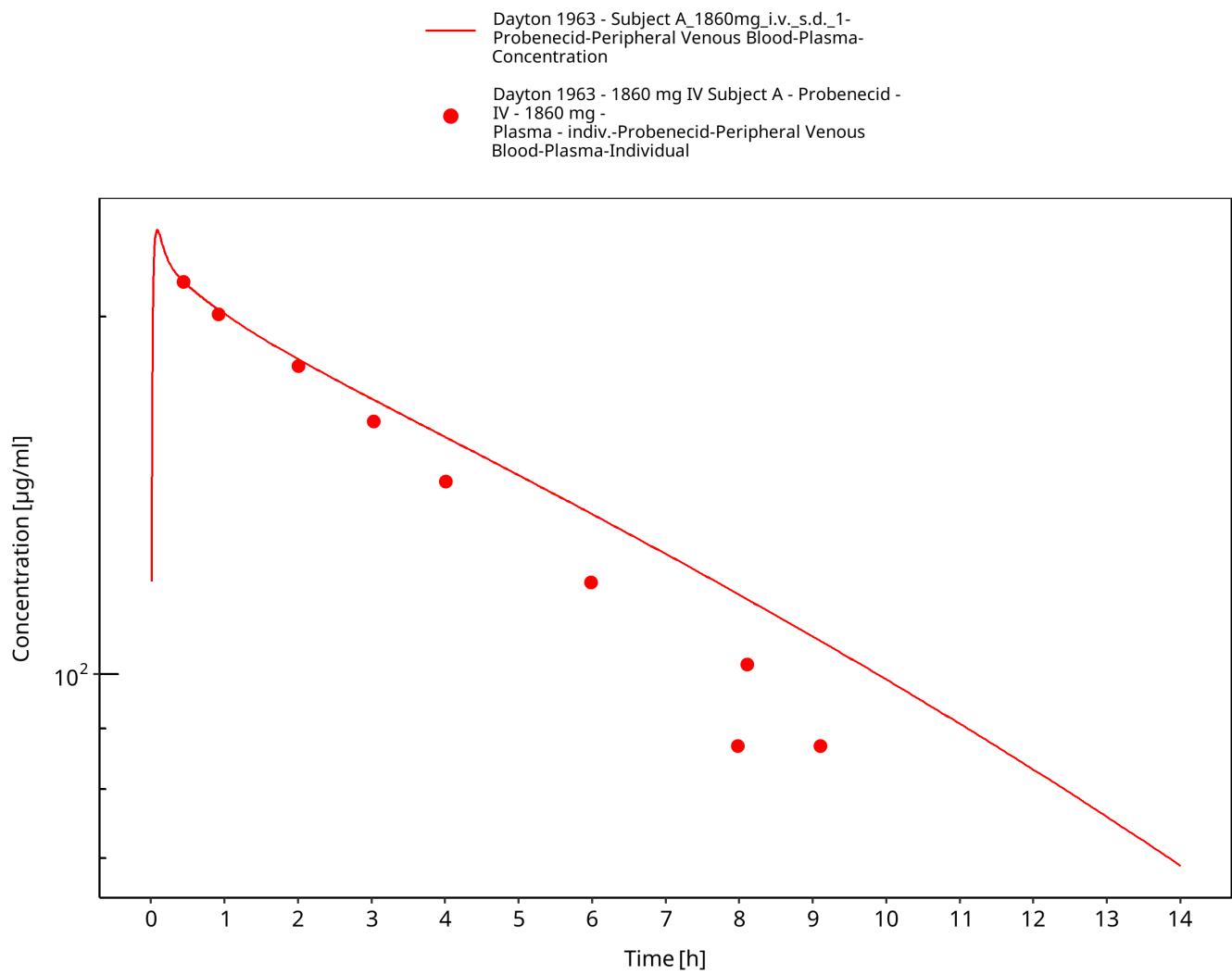
Figure 3-3: Dayton 1963 - 1860 mg IV Subject A
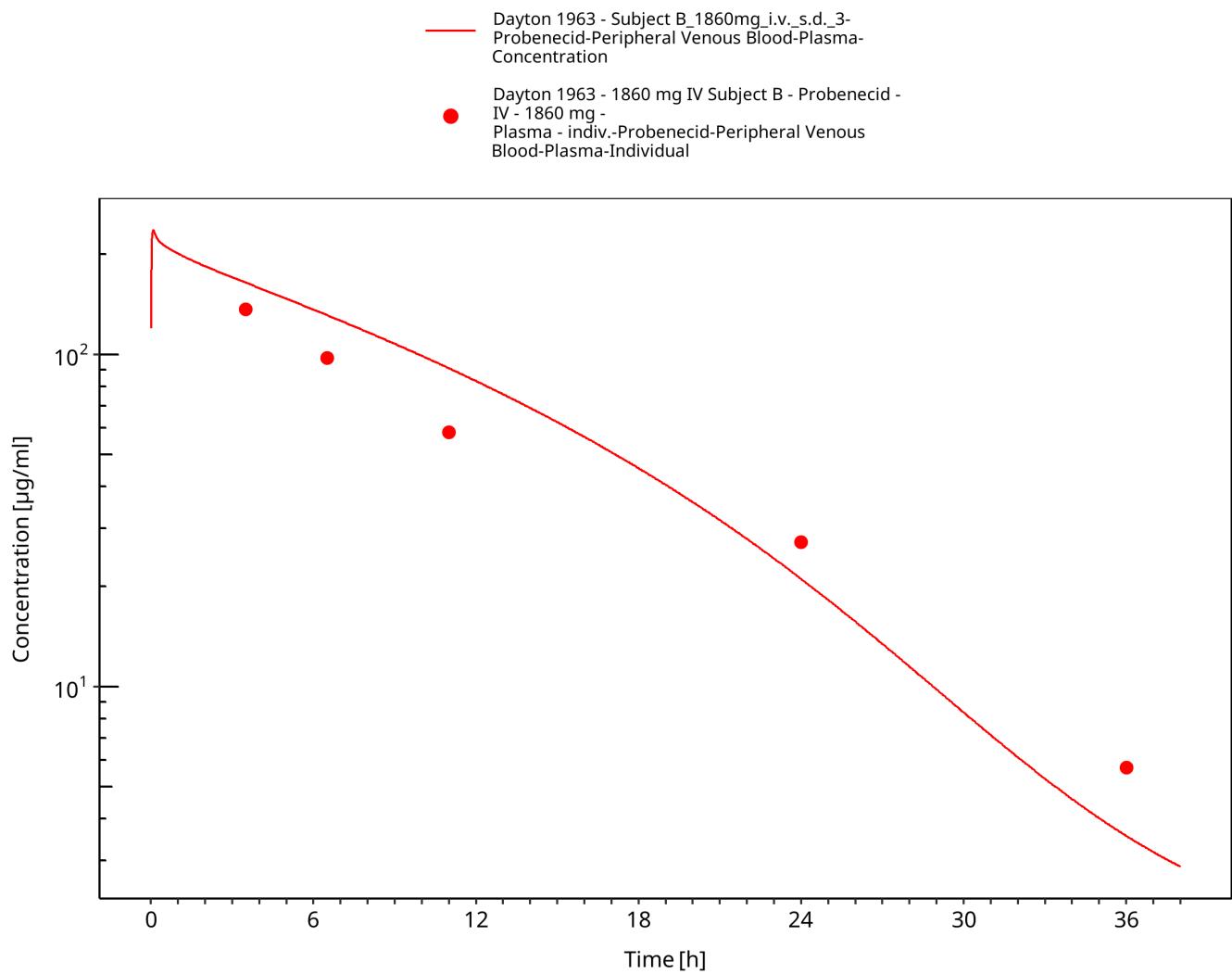
Figure 3-4: Dayton 1963 - 1860 mg IV Subject B
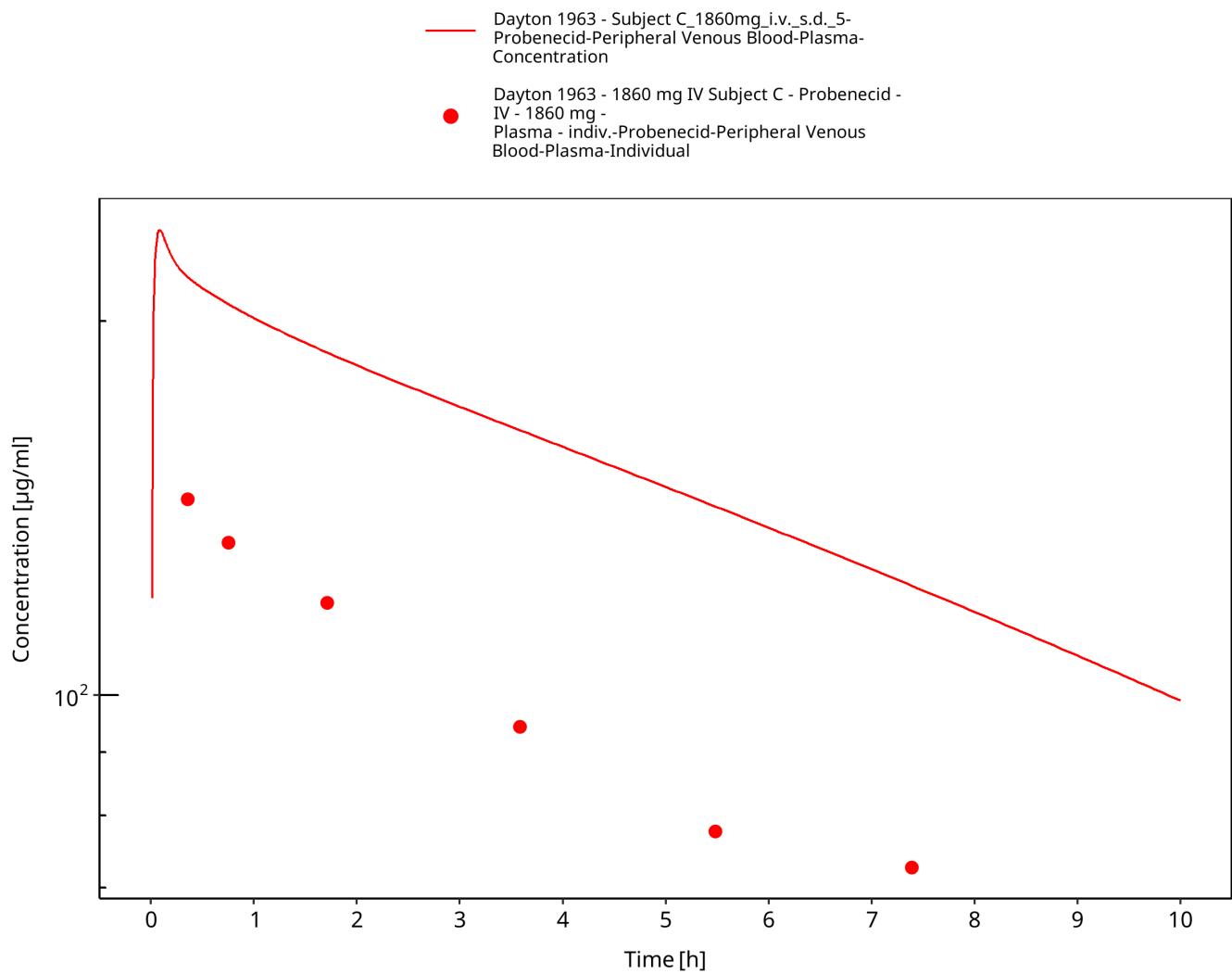
Figure 3-5: Dayton 1963 - 1860 mg IV Subject C
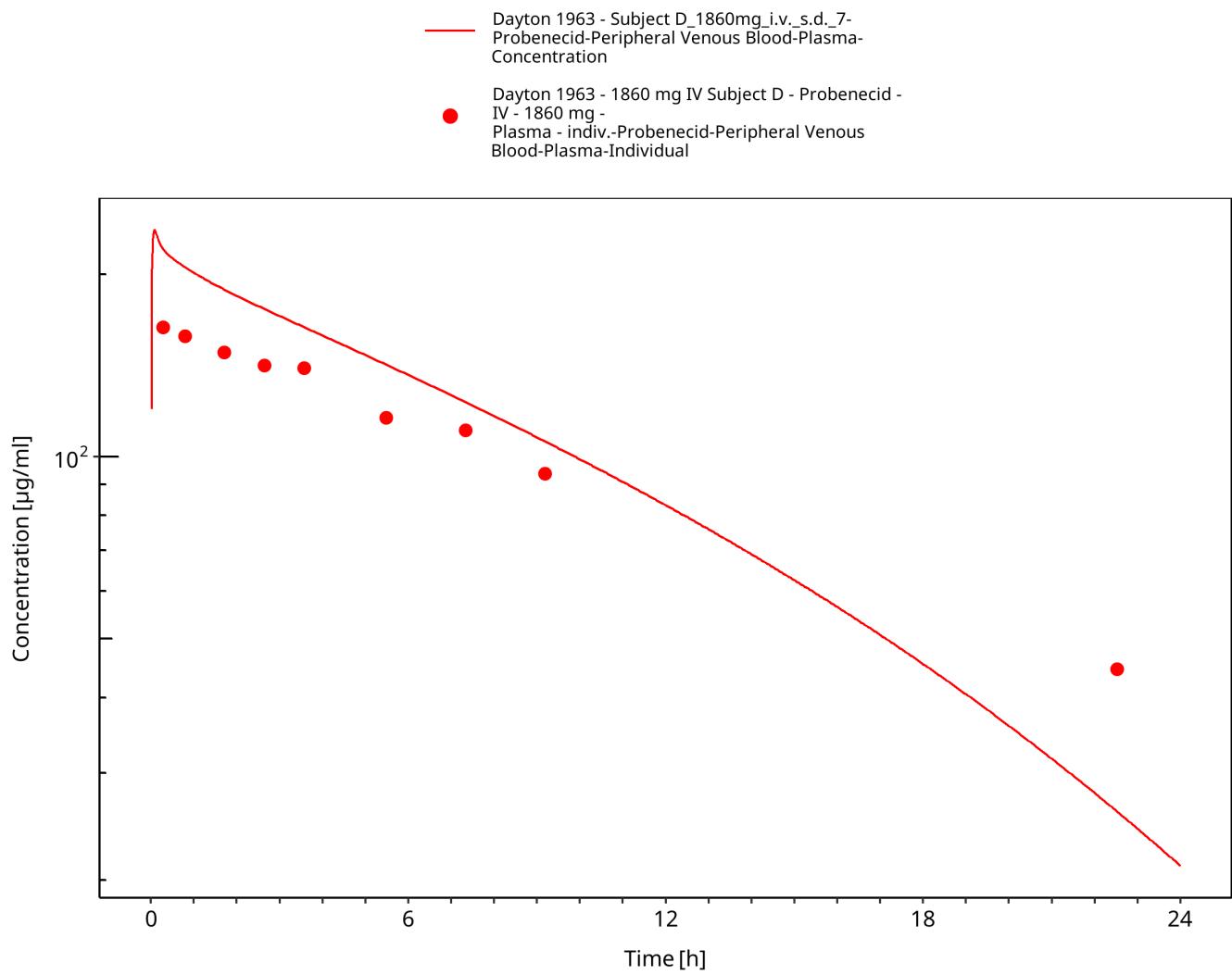
Figure 3-6: Dayton 1963 - 1860 mg IV Subject D
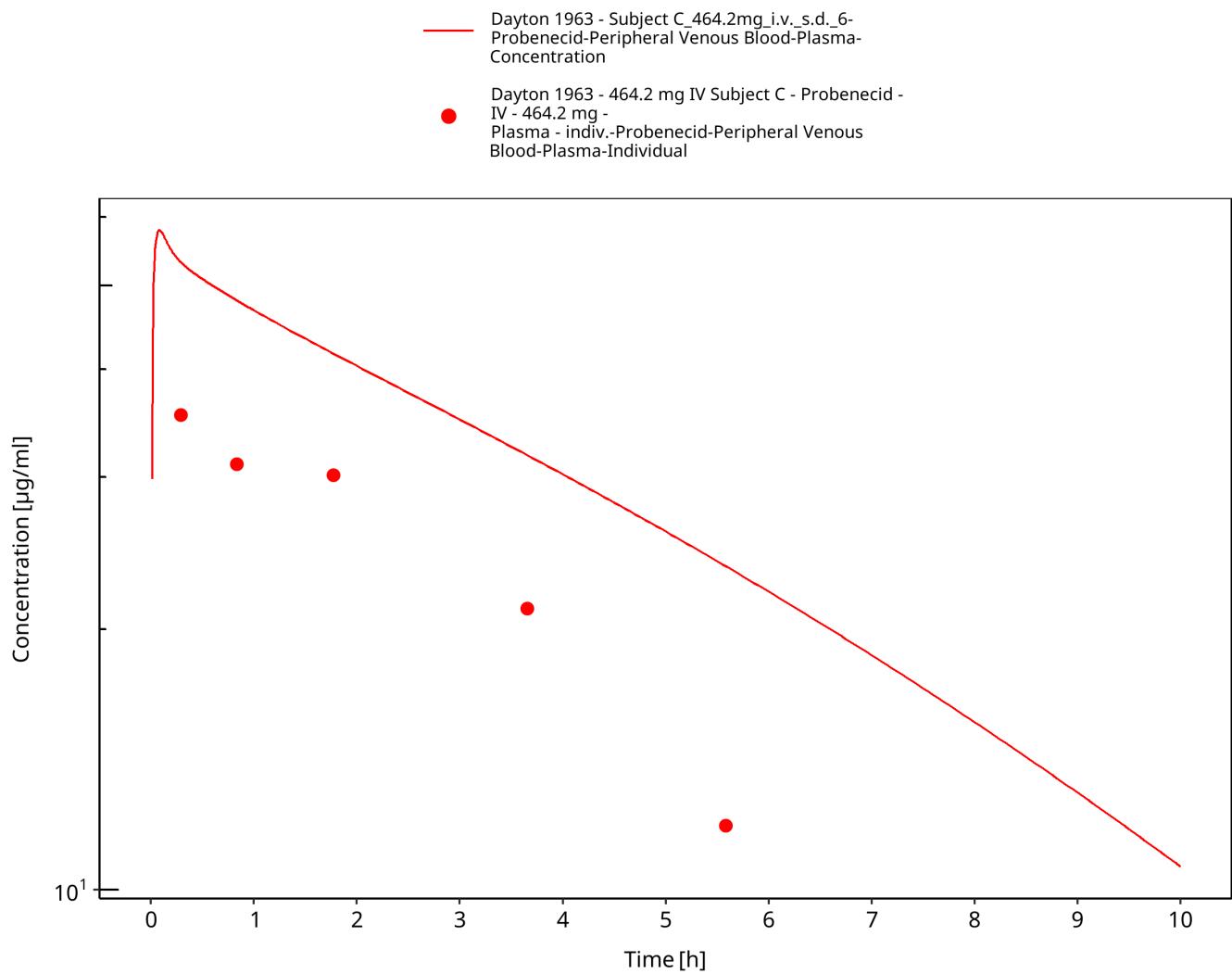
Figure 3-7: Dayton 1963 - 464.2 mg IV Subject C
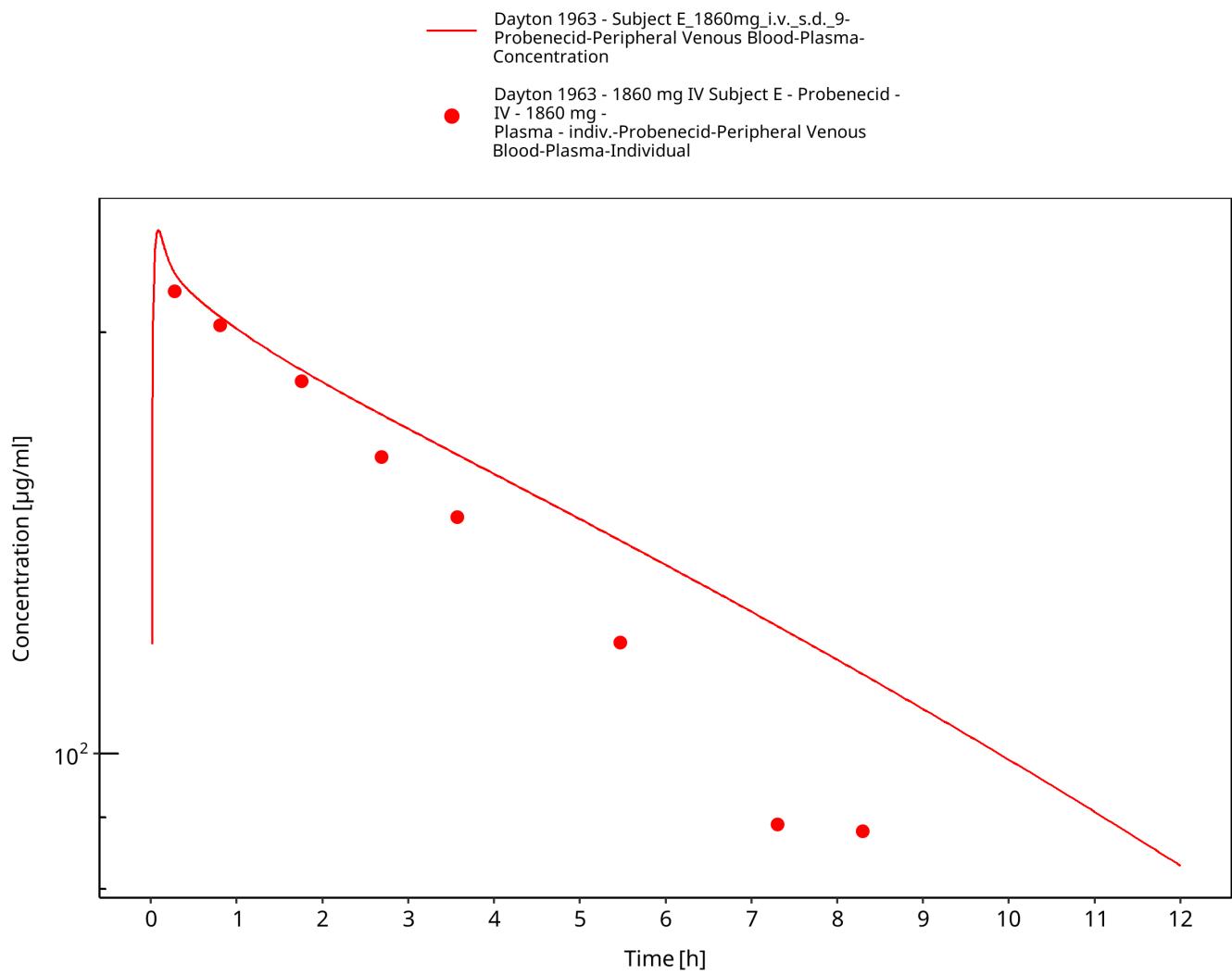
Figure 3-8: Dayton 1963 - 1860 mg IV Subject E

Dayton 1963 - Subject E_464.2mg_i.v._s.d._10-Probenecid-Peripheral Venous Blood-Plasma-Concentration

Dayton 1963 - 464.2 mg IV Subject E - Probenecid - IV - 464.2 mg - Plasma - indiv.-Probenecid-Peripheral Venous Blood-Plasma-Individual
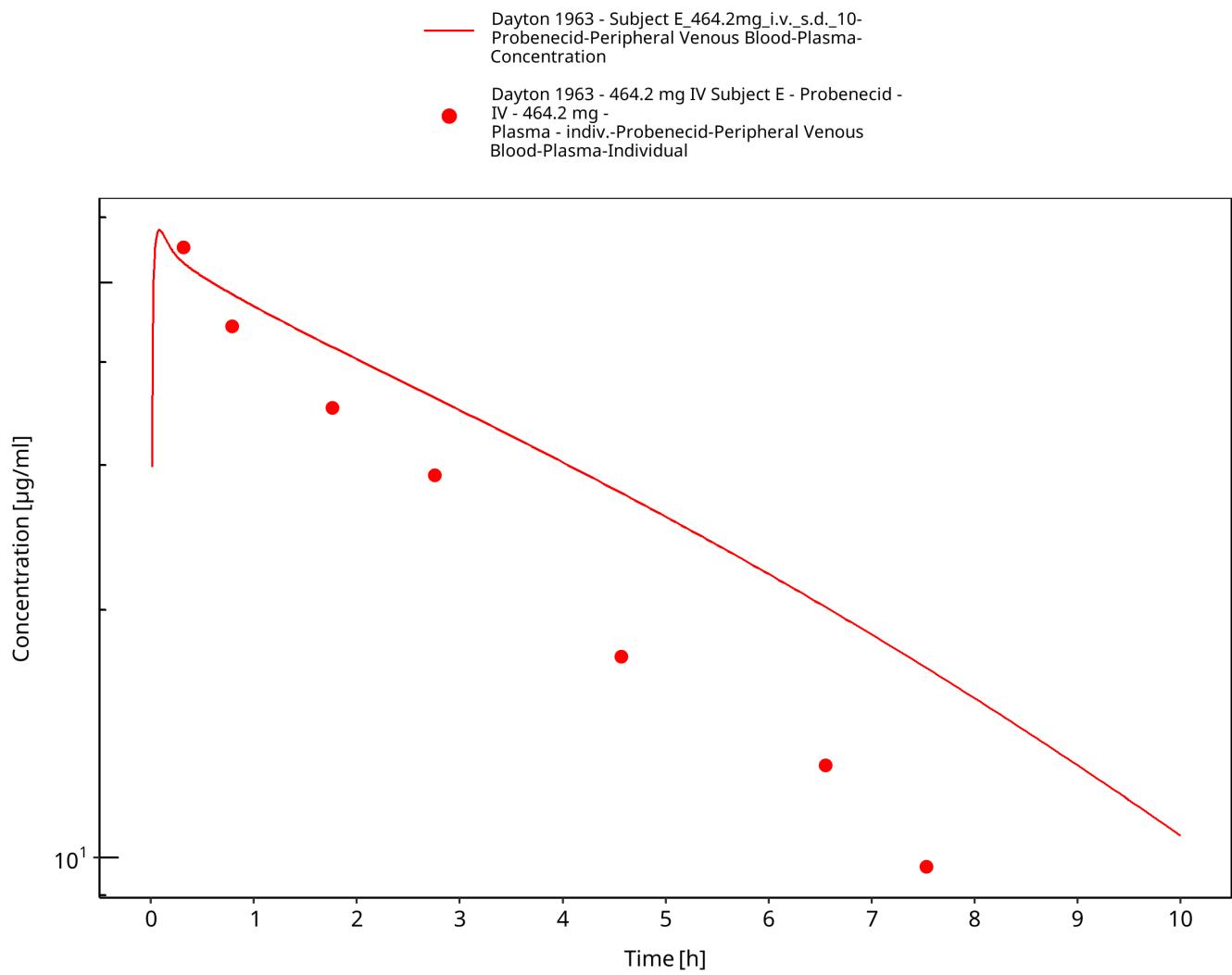
Figure 3-9: Dayton 1963 - 464.2 mg IV Subject E

Legend:

— Emanuelsson 1987_500mg_i.v._s.d._14-Probenecid-Peripheral Venous Blood-Plasma-Concentration

● Emanuelsson 1987 - 500 mg iv - Probenecid - IV - 500 mg - Plasma - agg. (n=6)-Probenecid-Peripheral Venous Blood-Plasma-ArithmeticMean
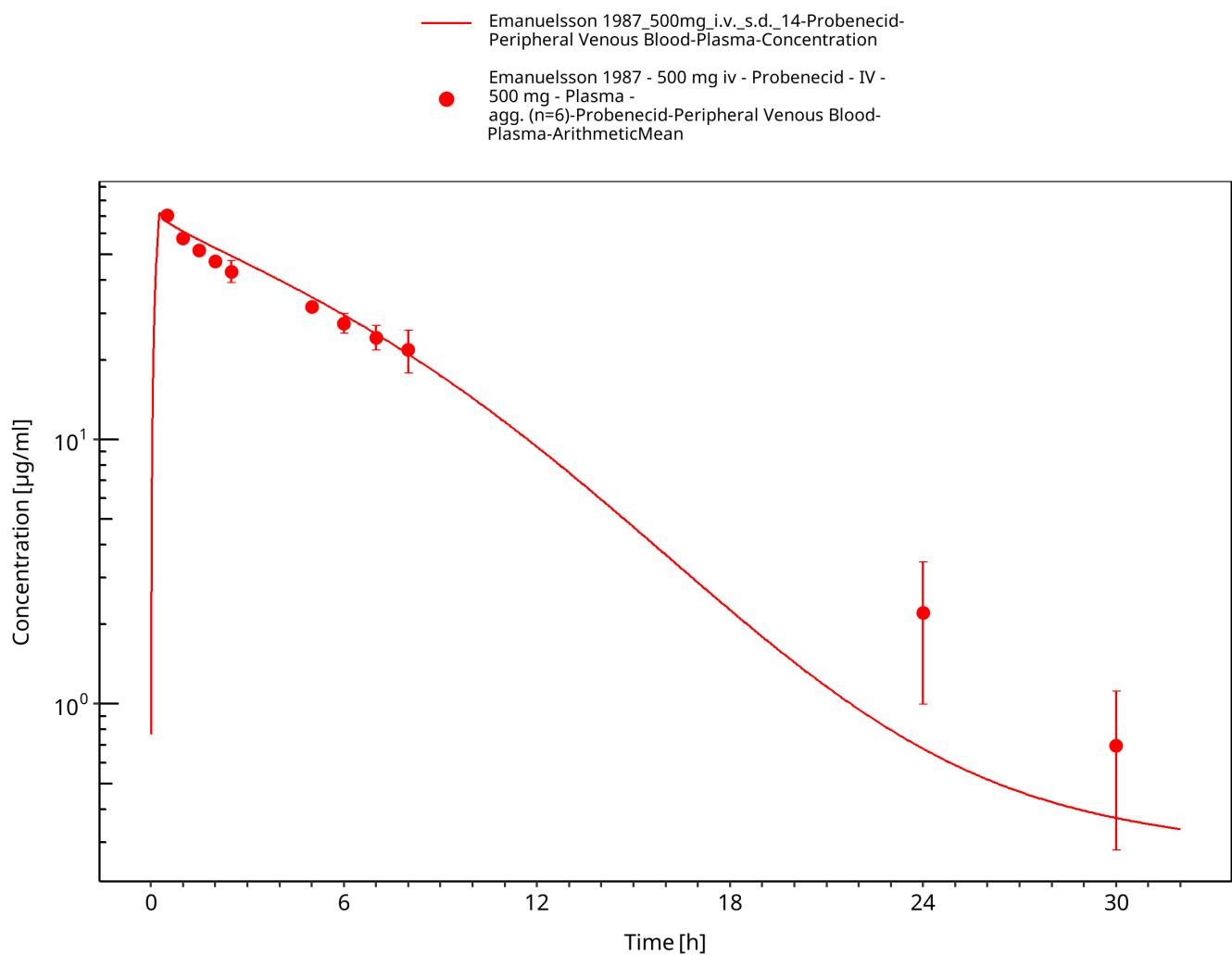
Figure 3-10: Emanuelsson 1987 - 500 mg iv
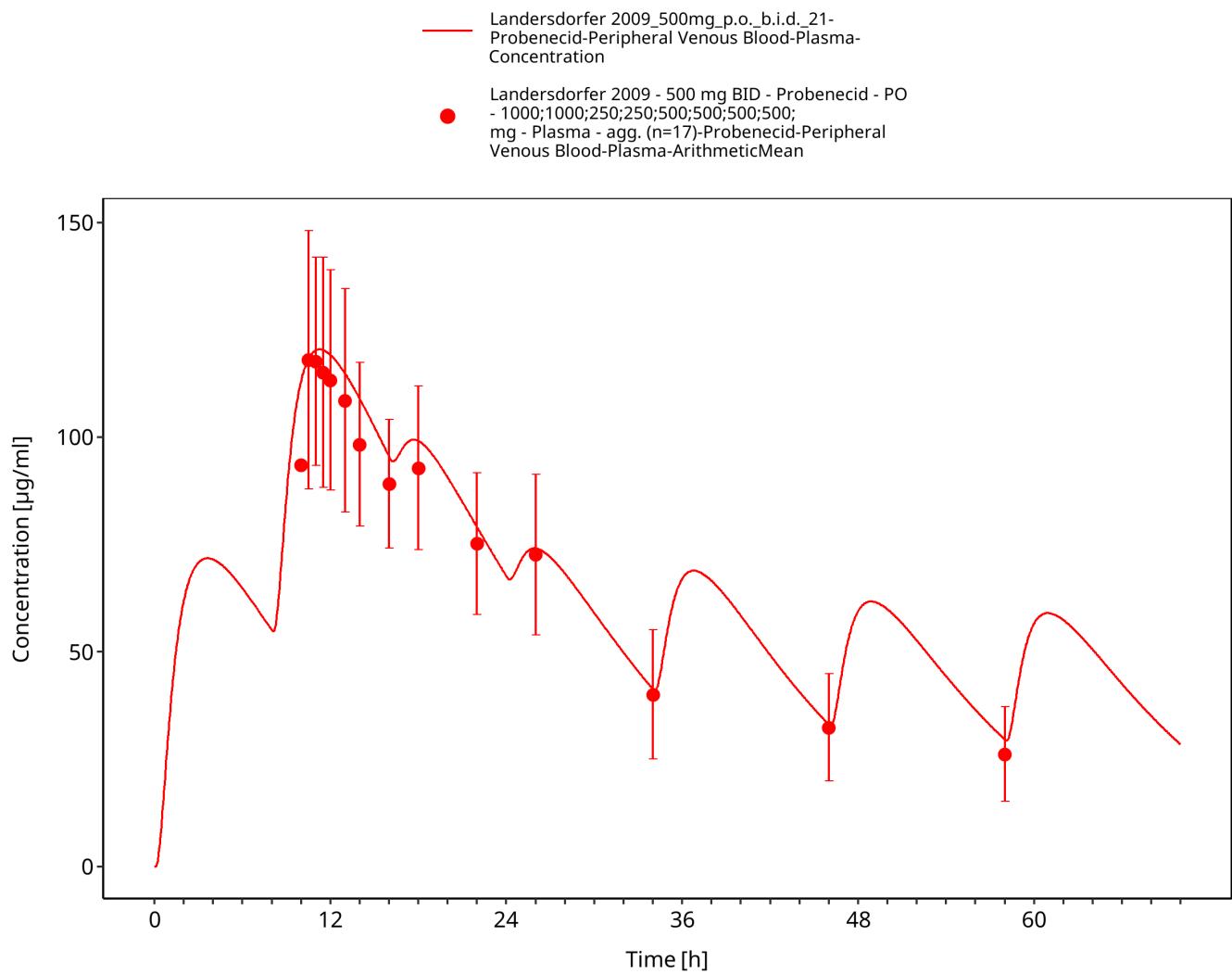
Figure 3-11: Landersdorfer 2009 - 500 mg BID
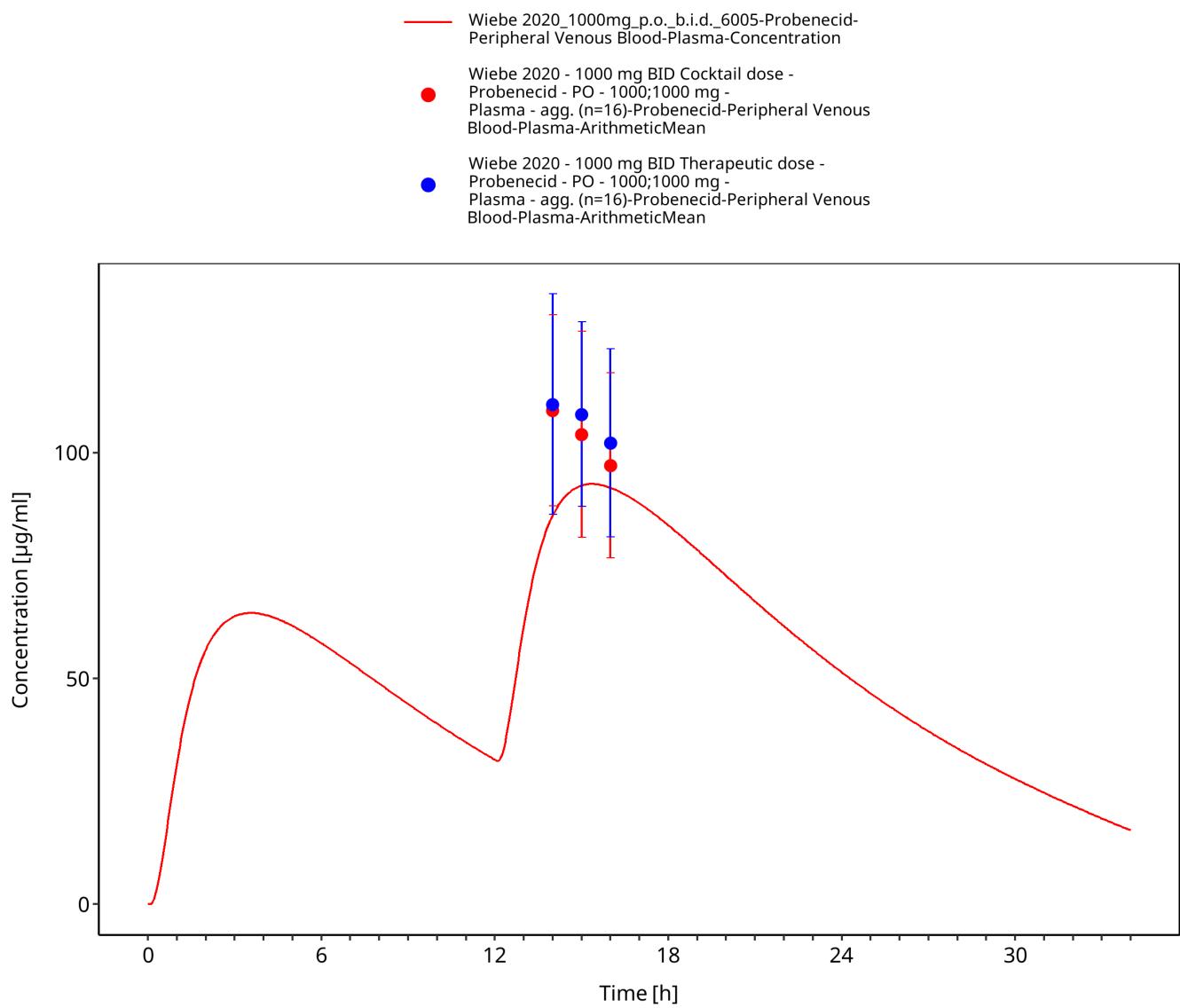
Figure 3-12: Wiebe 2020 - 1000 mg BID
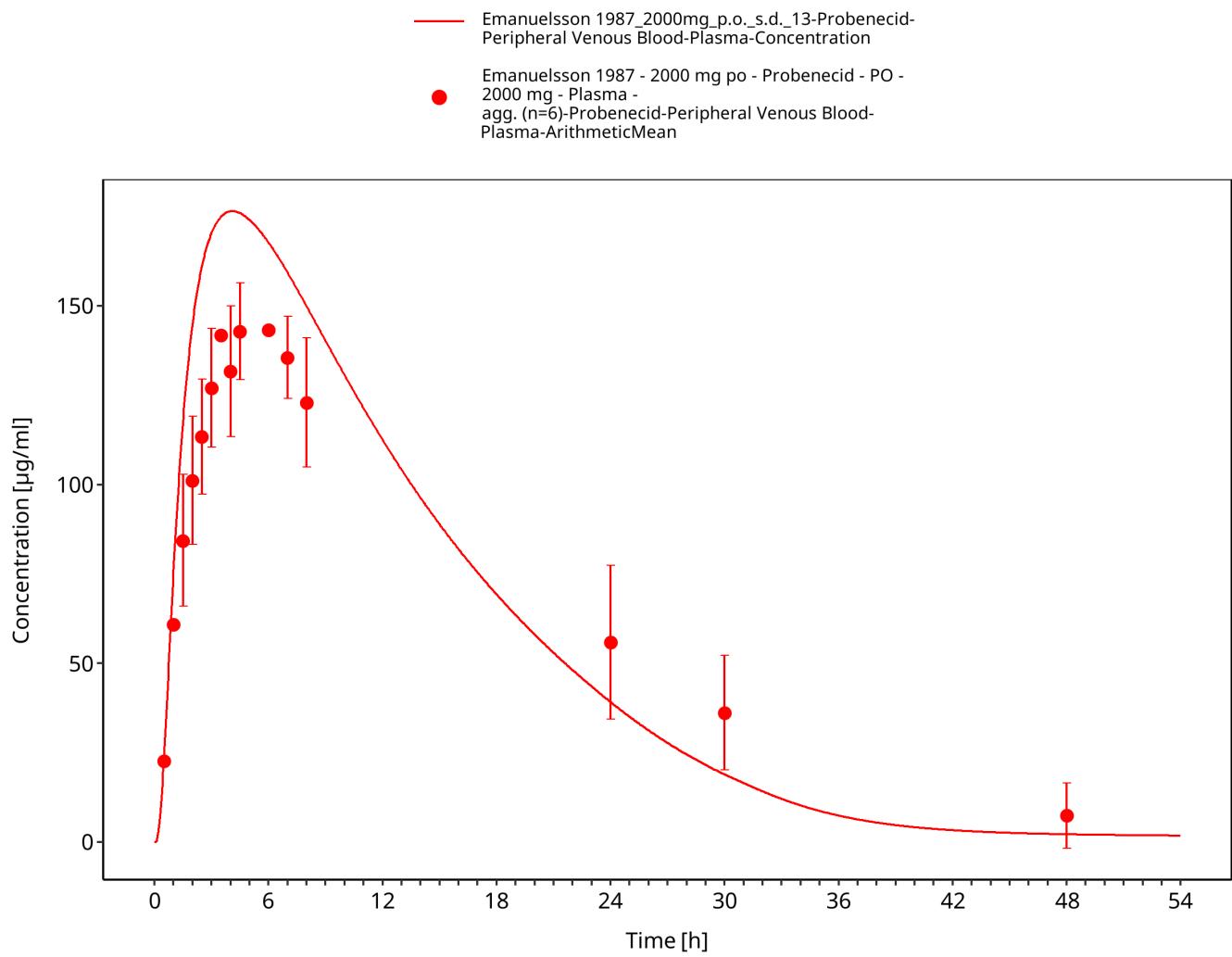
Figure 3-13: Emanuelsson 1987 - 2000 mg po
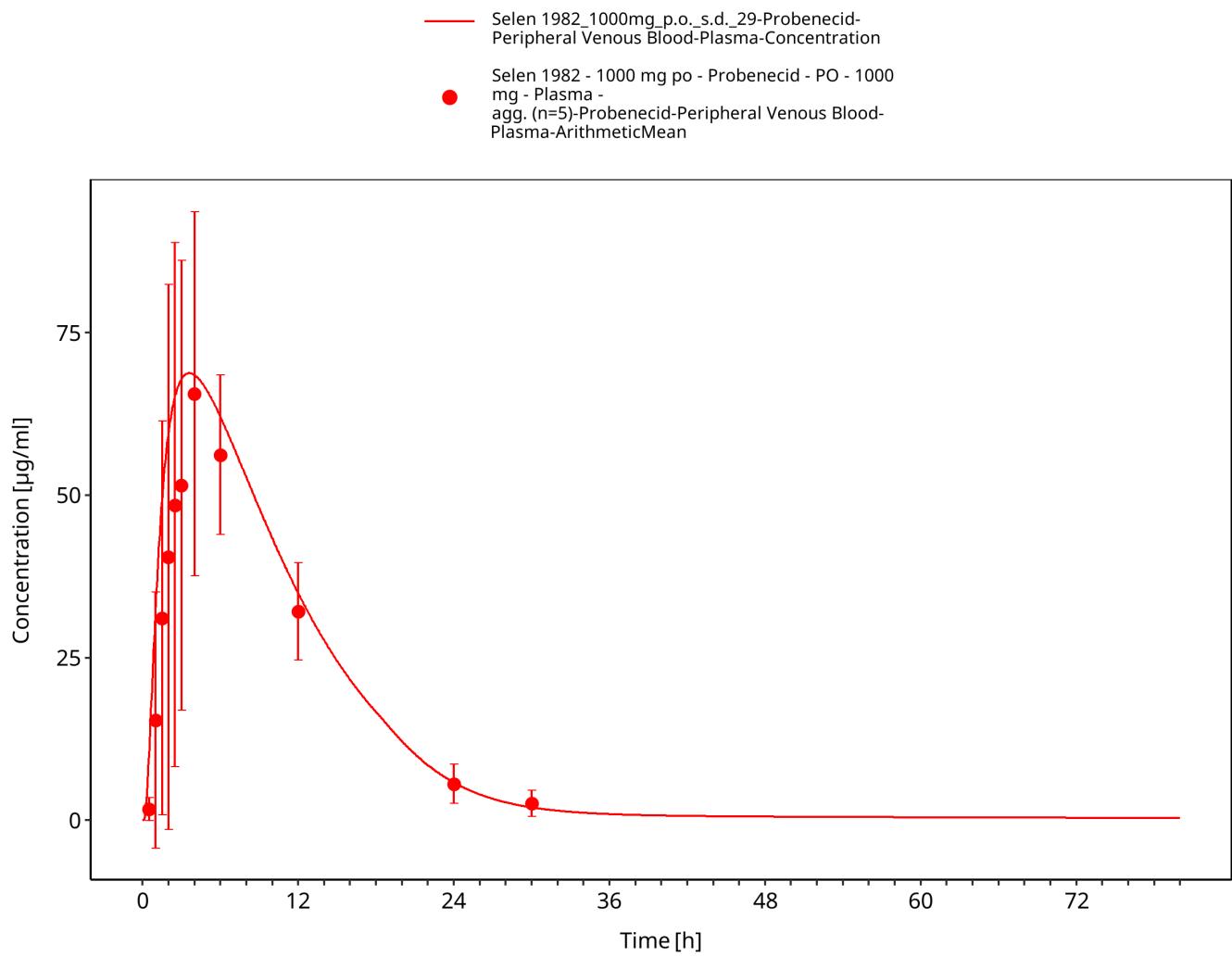
Figure 3-14: Selen 1982 - 1000 mg po
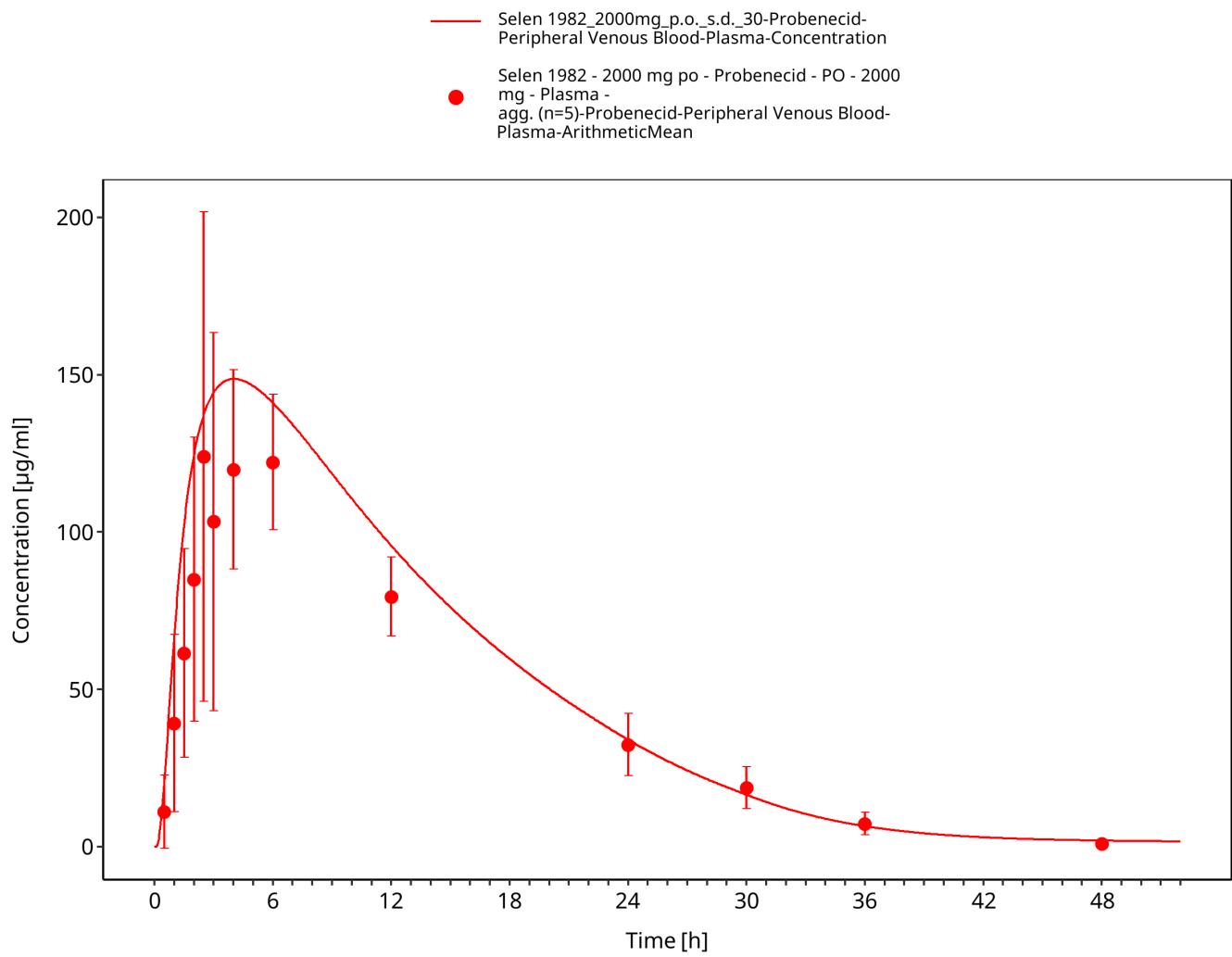
Figure 3-15: Selen 1982 - 2000 mg po
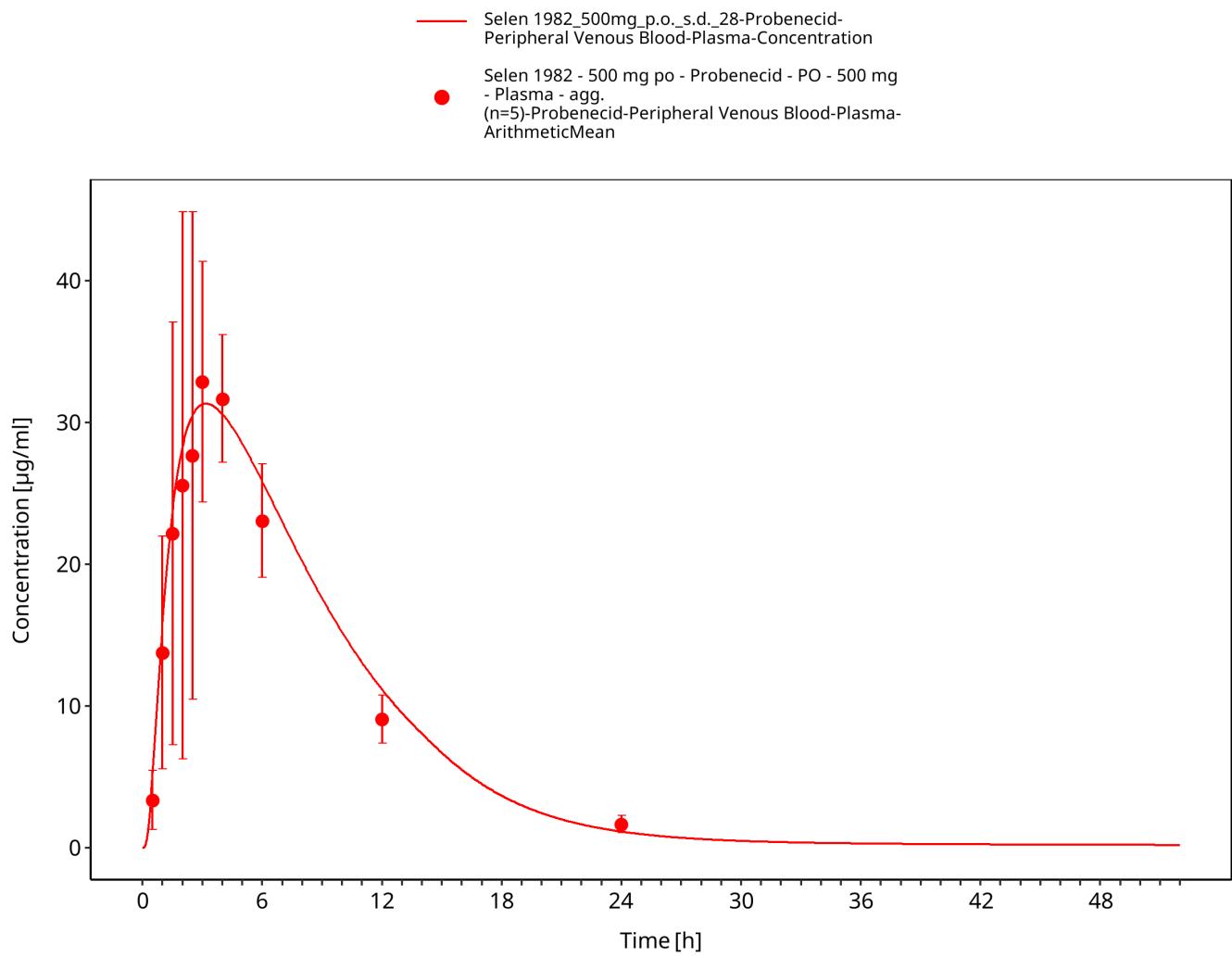
Figure 3-16: Selen 1982 - 500 mg po
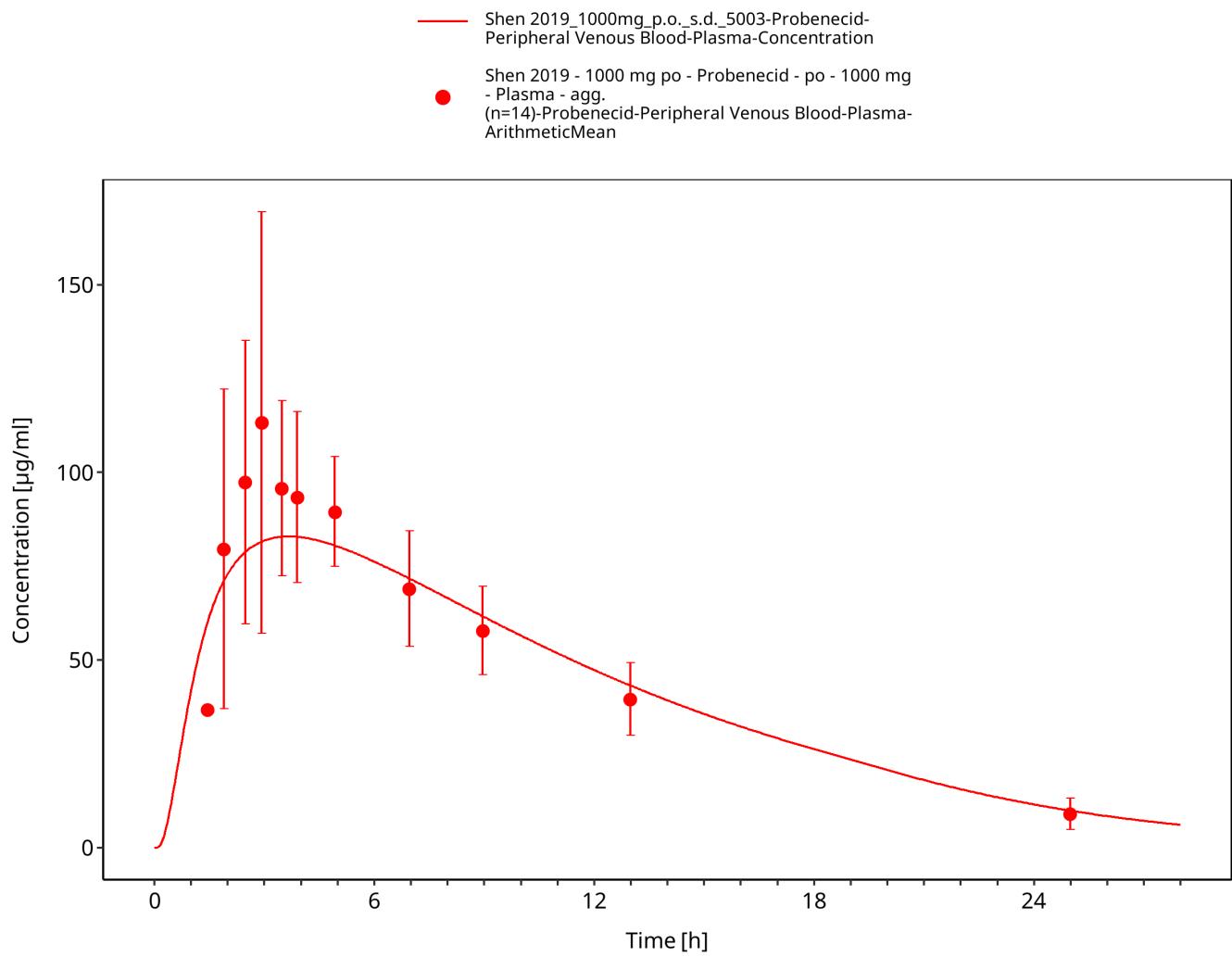
Figure 3-17: Shen 2019 - 1000 mg po
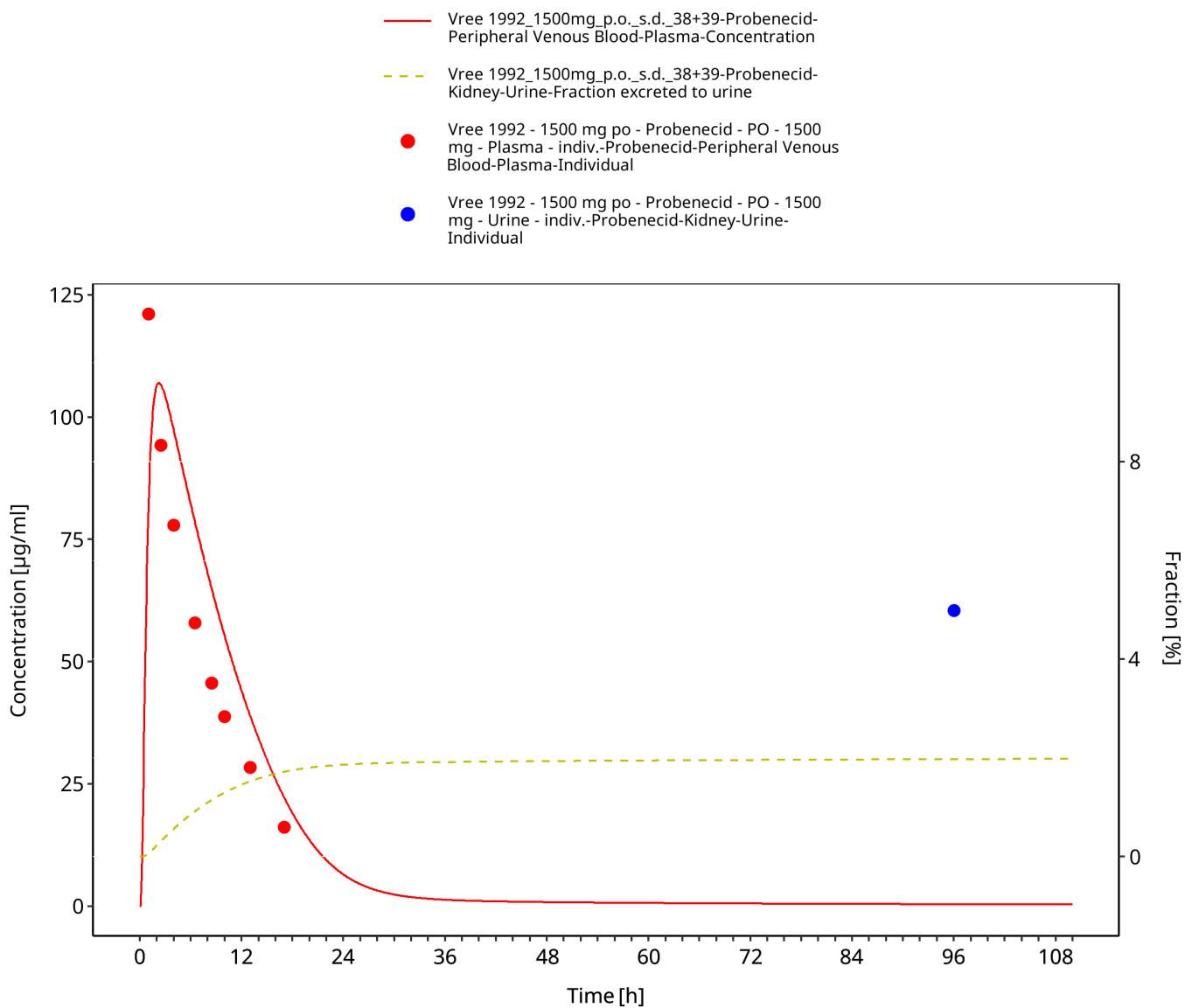
Figure 3-18: Vree 1992 - 1500 mg po
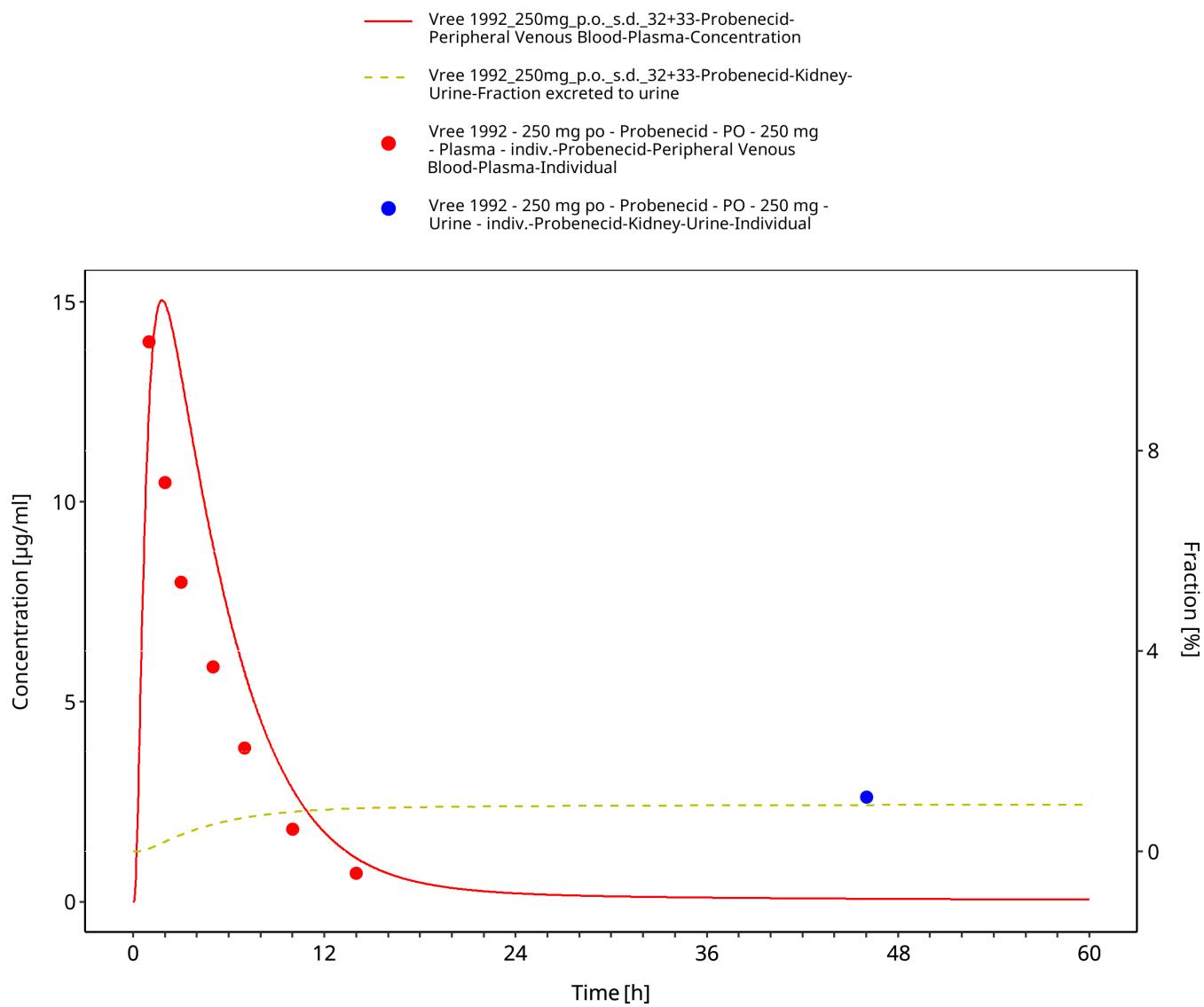
**Figure 3-19: Vree 1992 - 250 mg po**

3.3.2 Model Verification
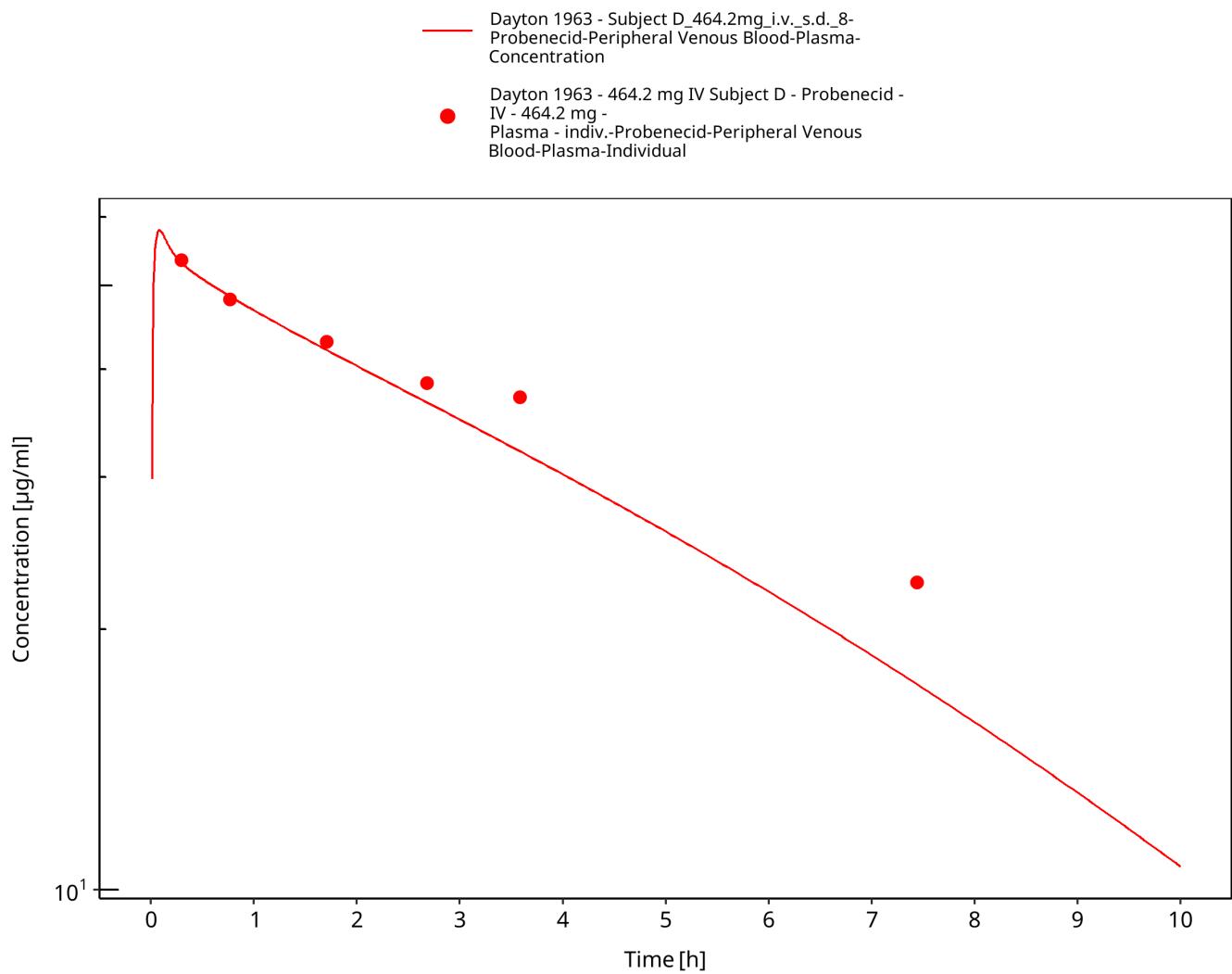
Figure 3-20: Dayton 1963 - 464.2 mg IV Subject D - Probenecid - IV - 464.2 mg - Plasma - indiv.
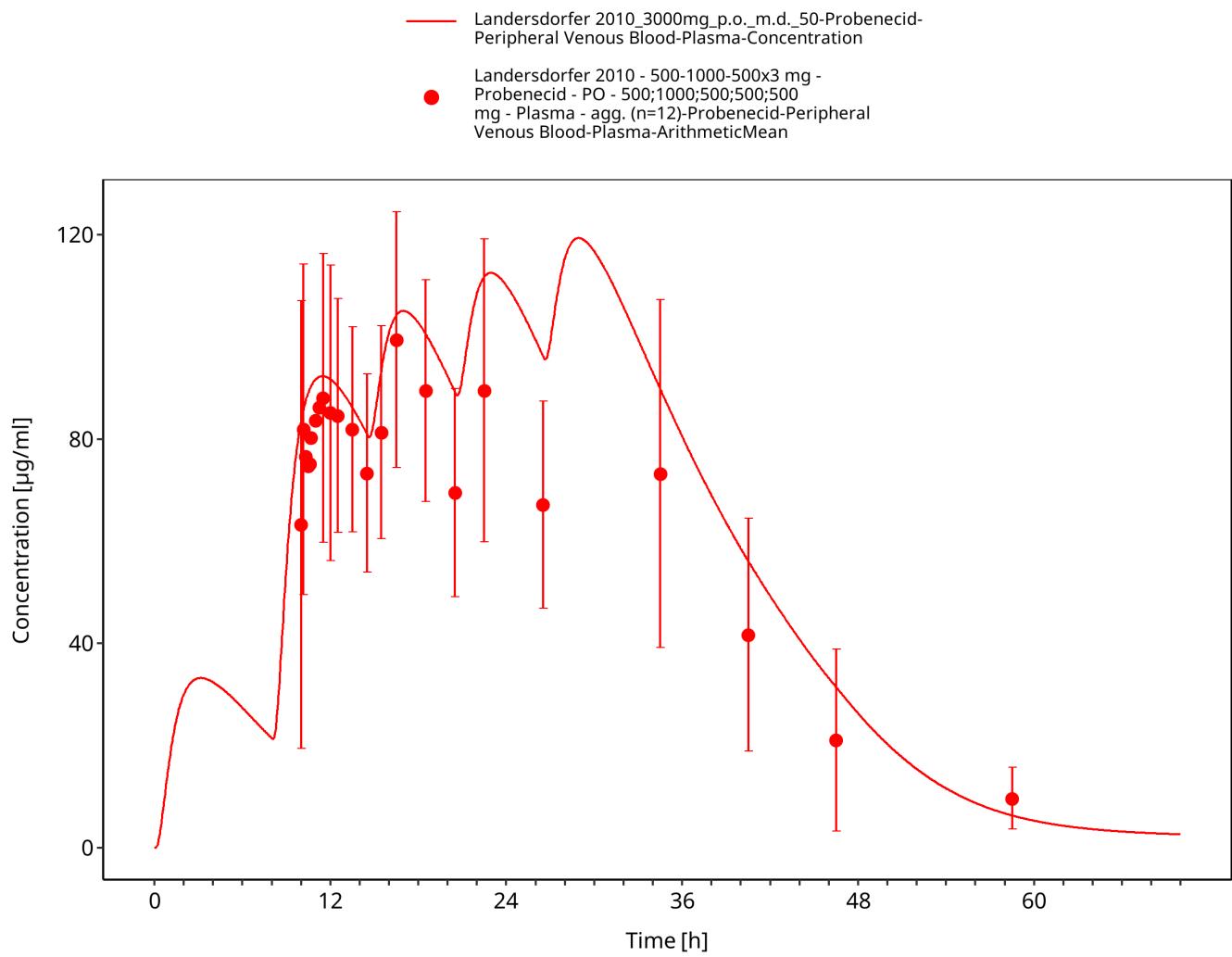
**Figure 3-21: Landersdorfer 2010 - 500-1000-500x3 mg**
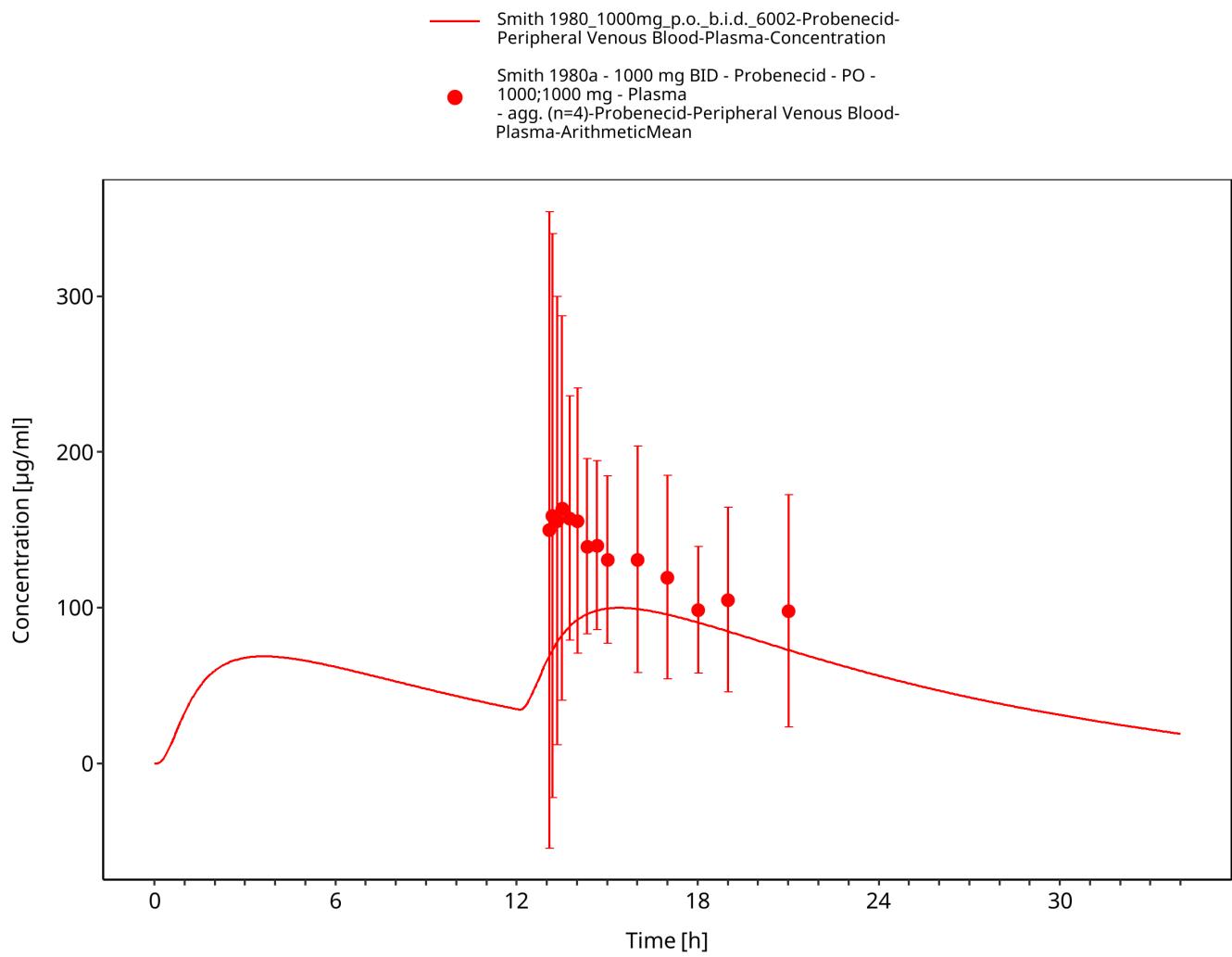
**Figure 3-22: Smith 1980a - 1000 mg BID**
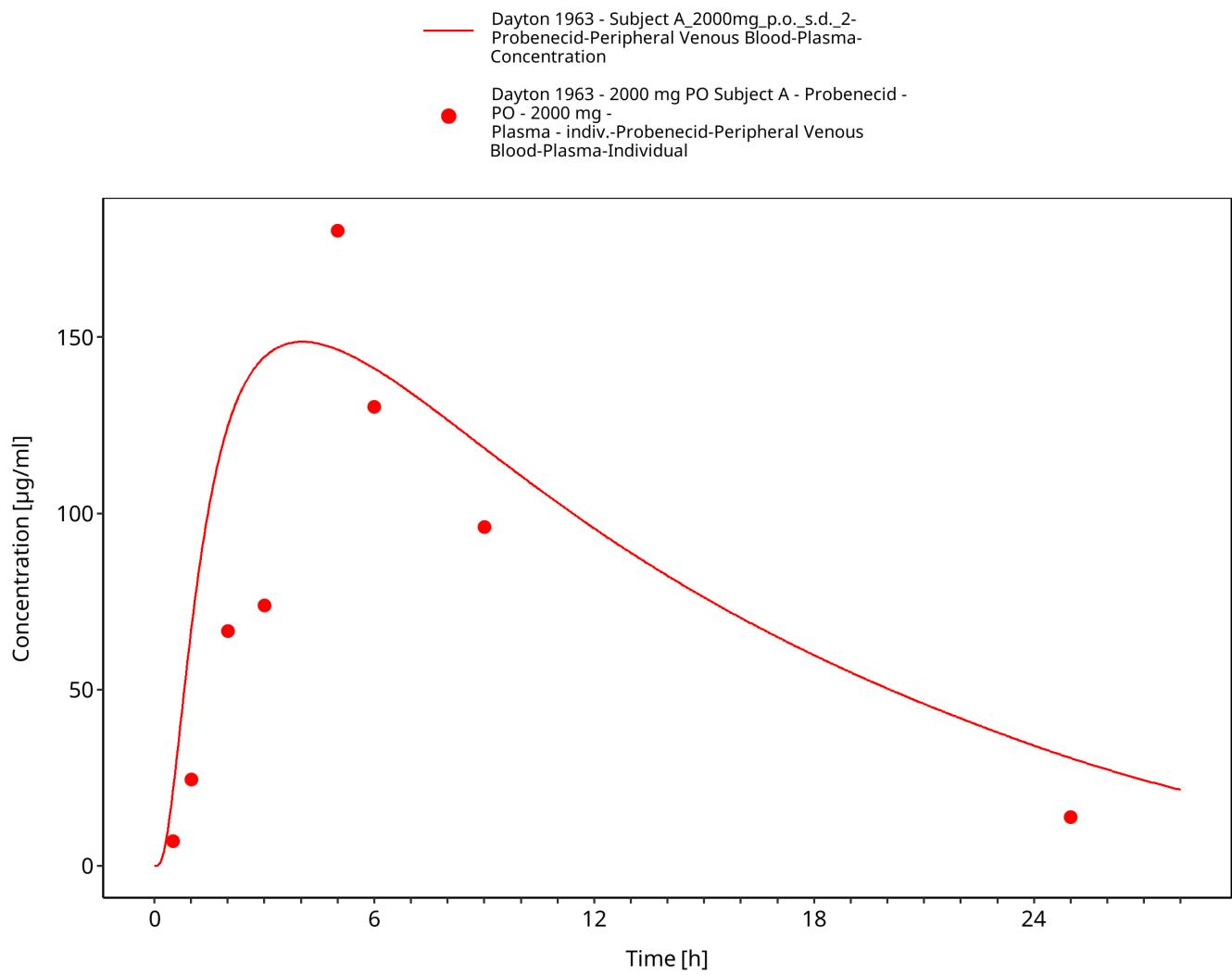
**Figure 3-23: Dayton 1963 - 2000 mg PO Subject A**
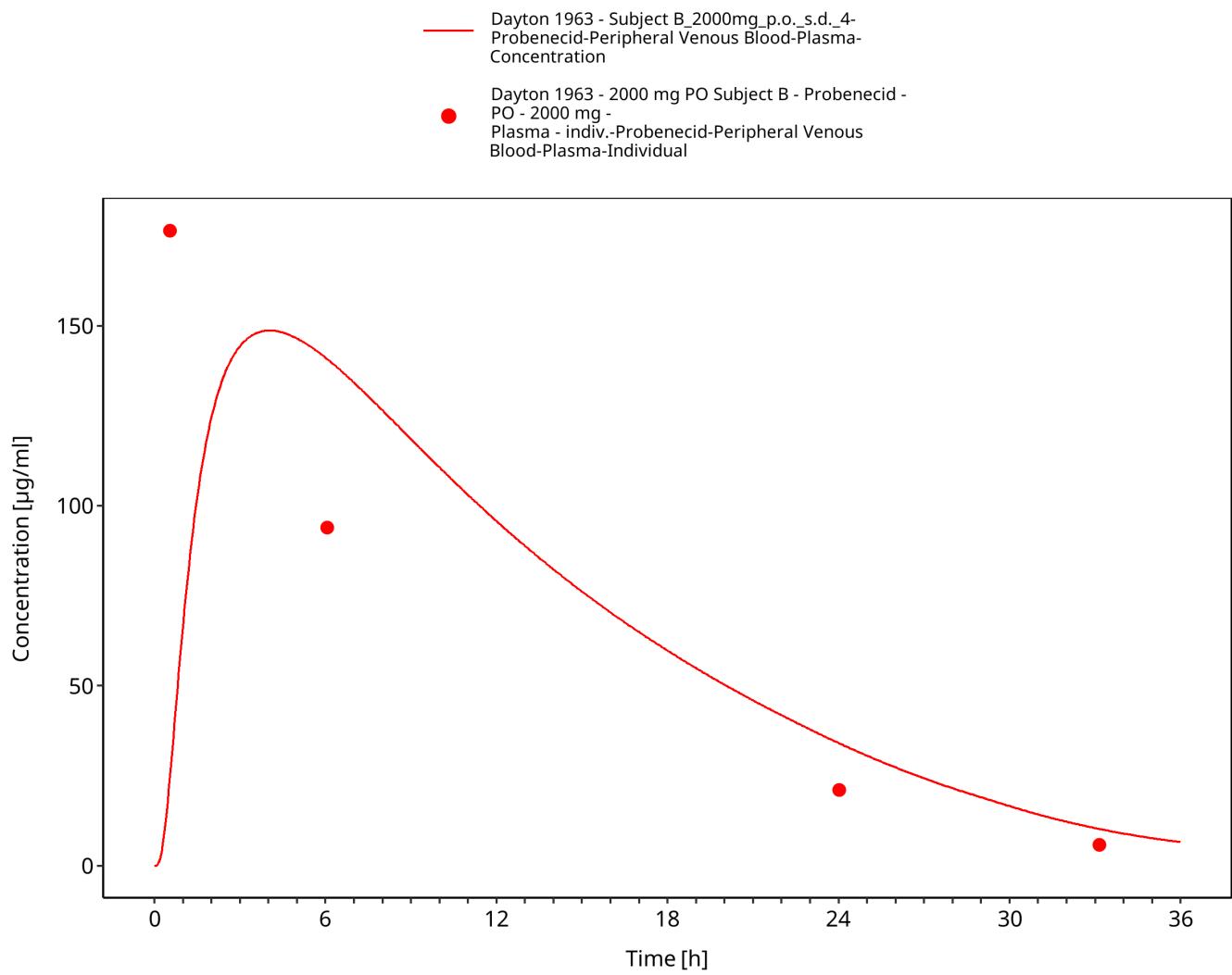
Figure 3-24: Dayton 1963 - 2000 mg PO Subject B
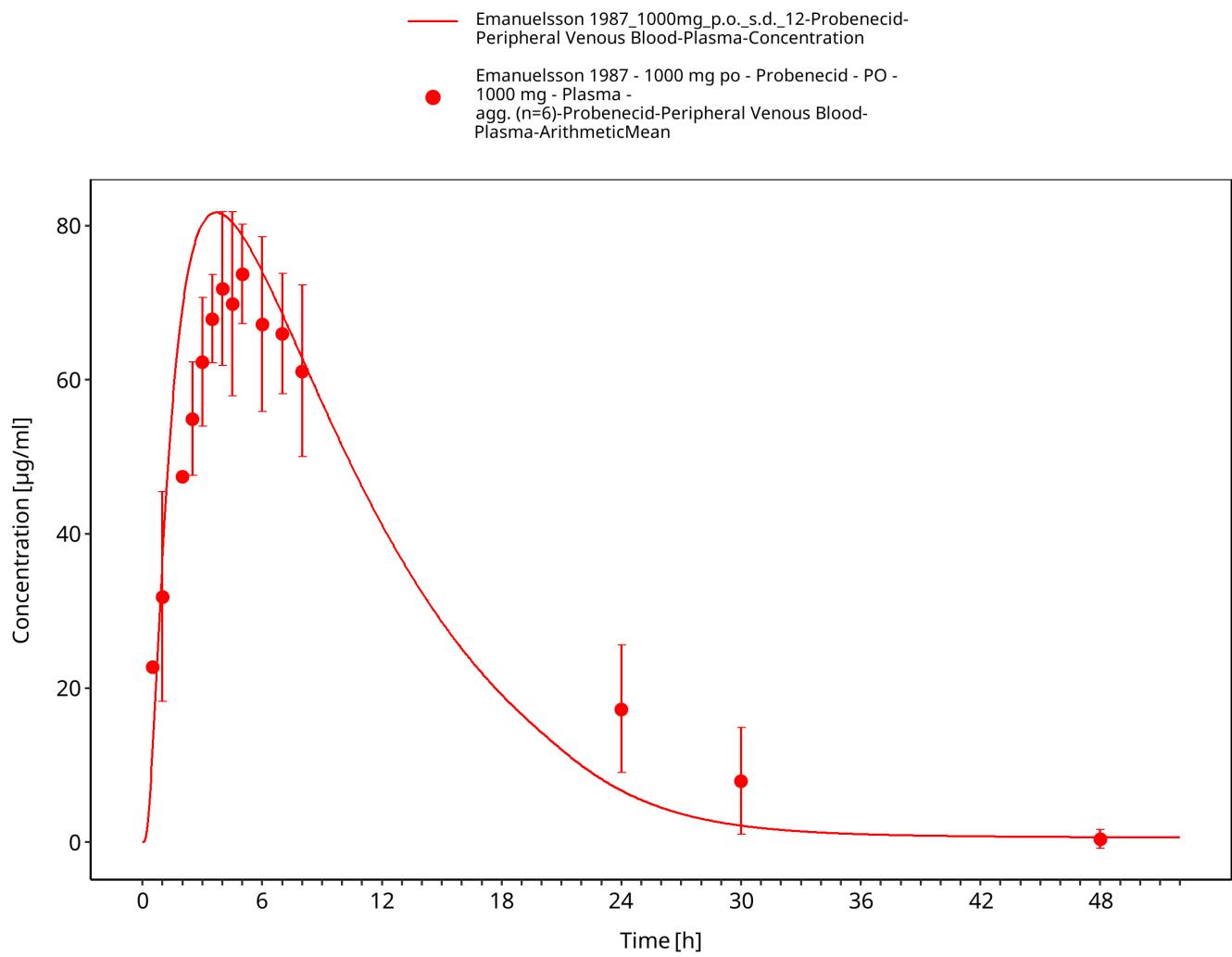
Figure 3-25: Emanuelsson 1987 - 1000 mg po
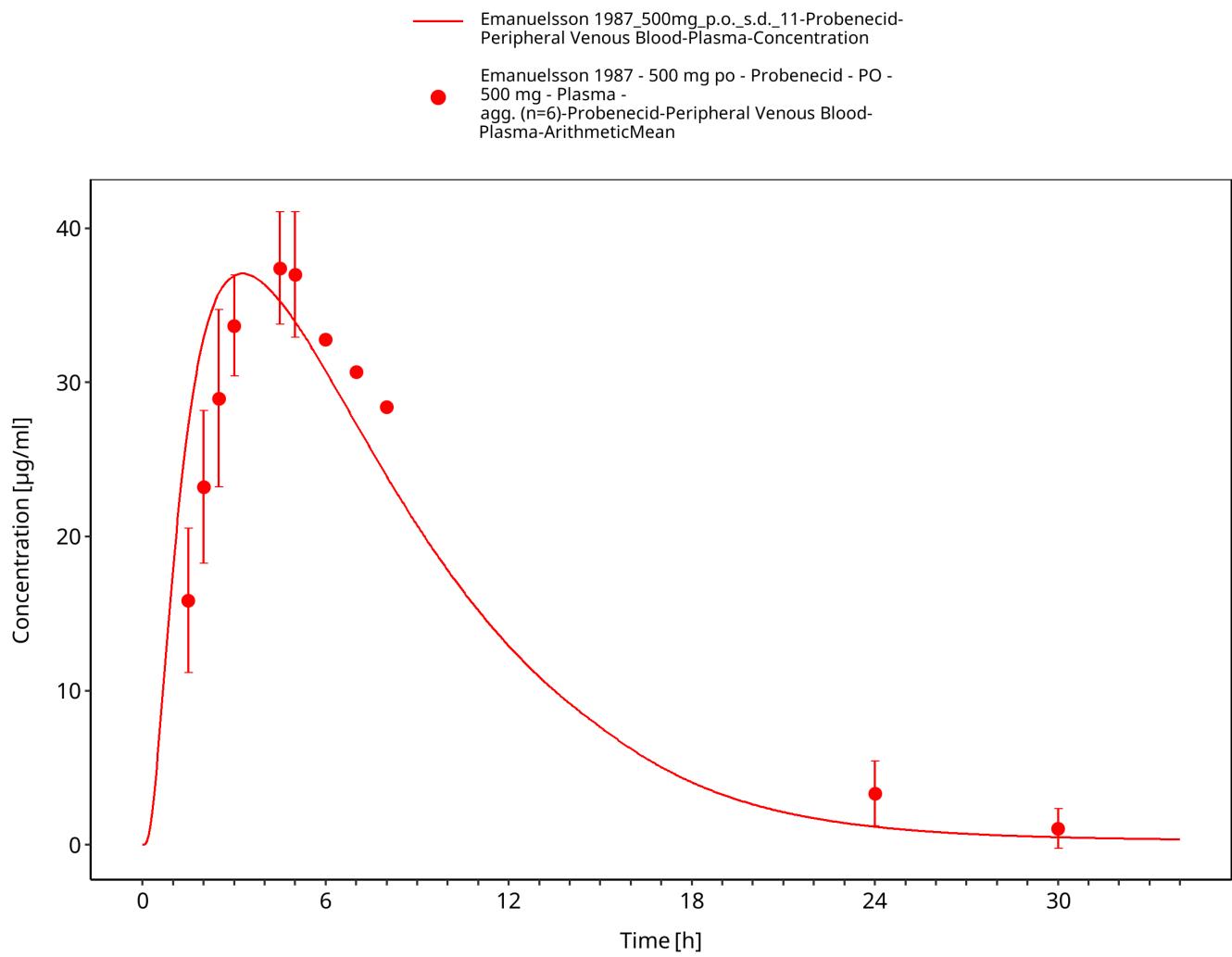
**Figure 3-26: Emanuelsson 1987 - 500 mg po**
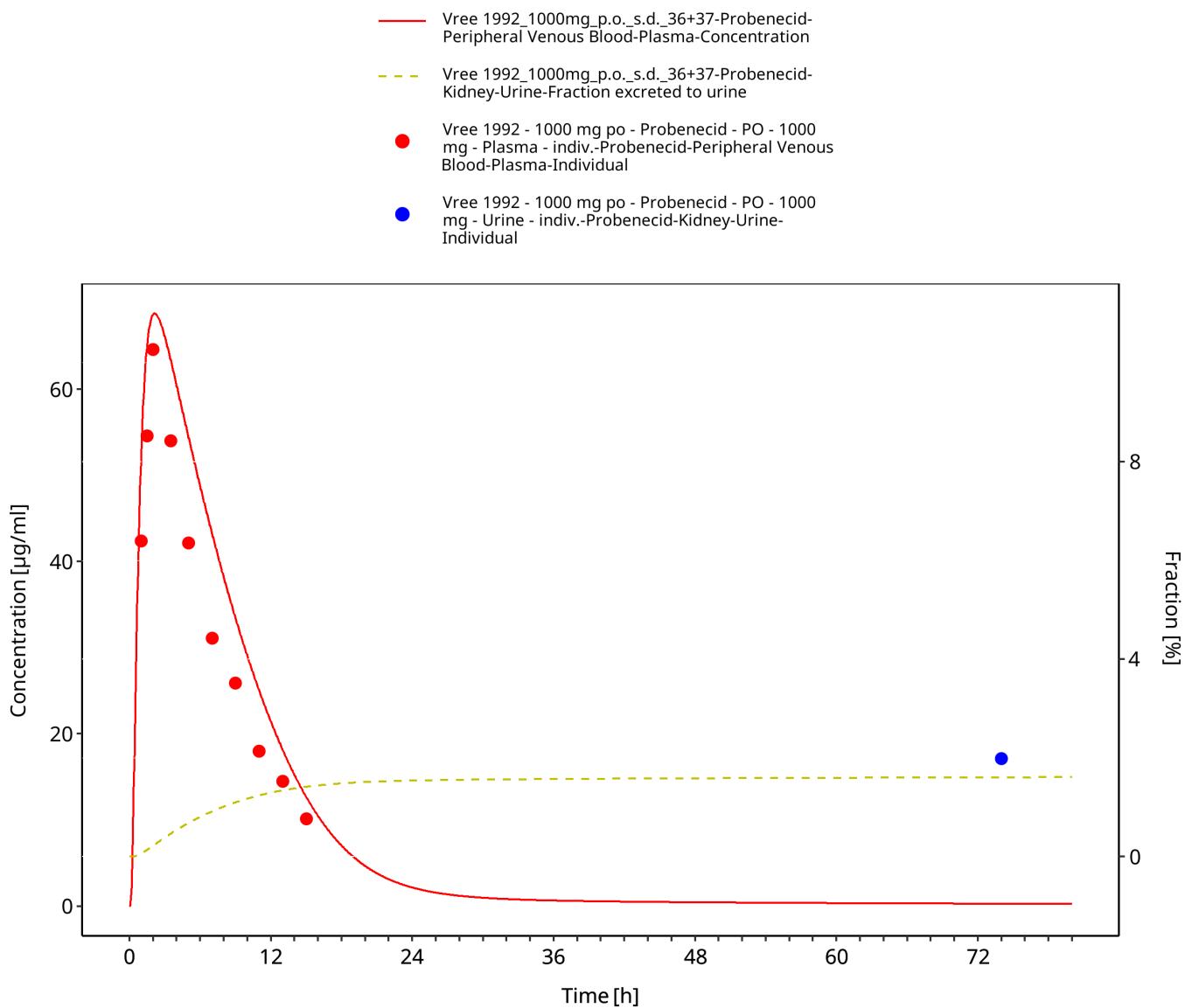
**Figure 3-27: Vree 1992 - 1000 mg po**
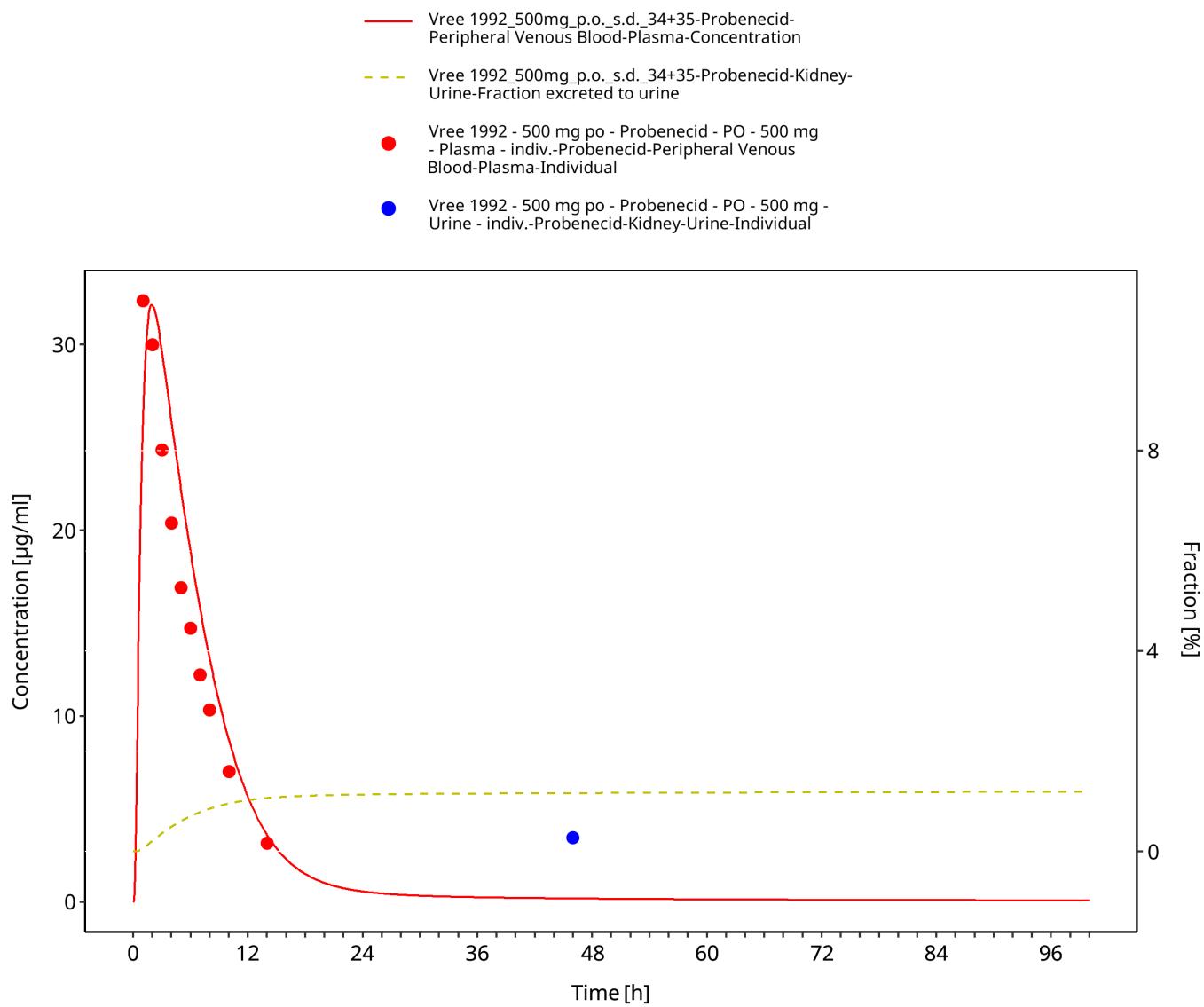
Figure 3-28: Vree 1992 - 500 mg po
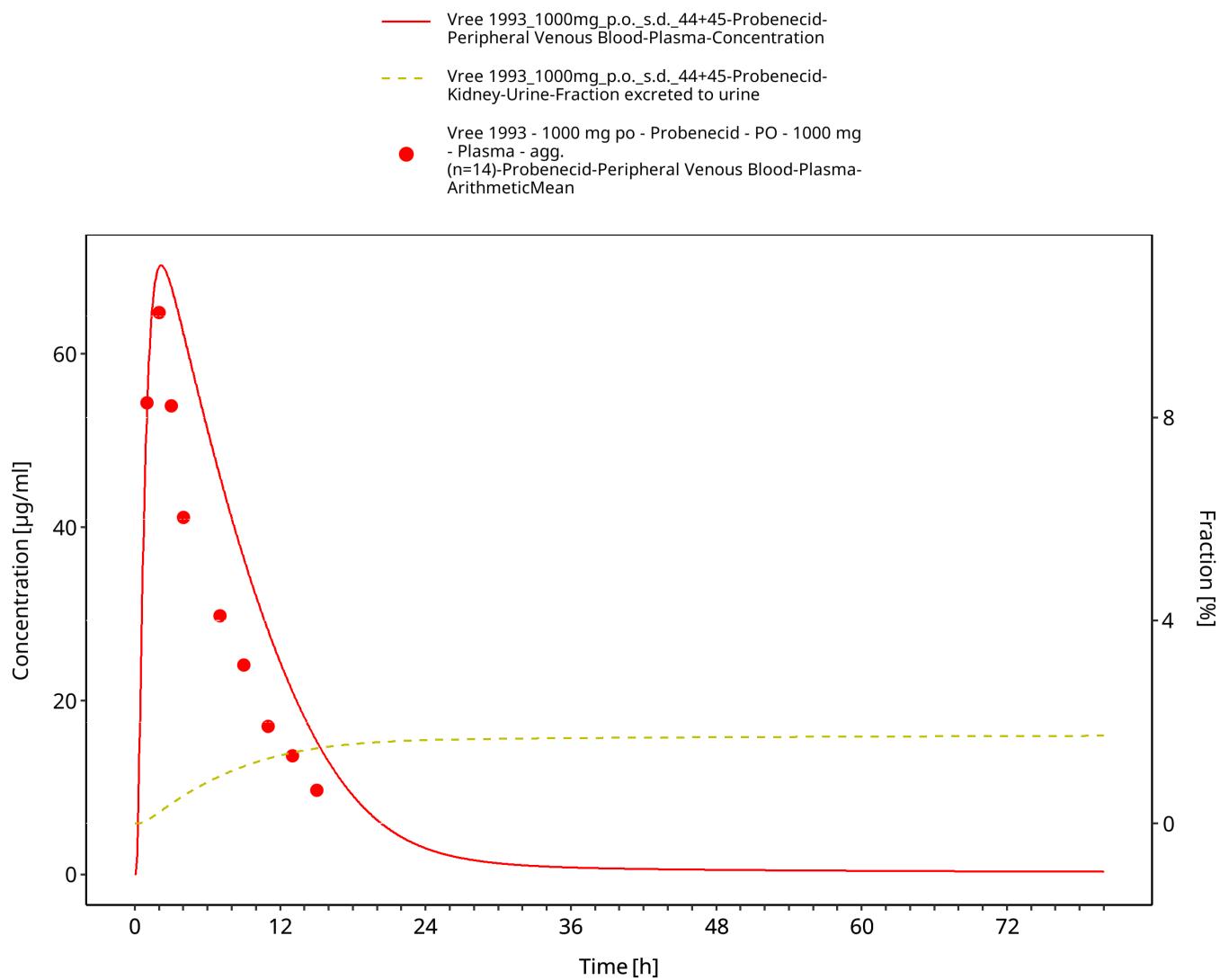
Figure 3-29: Vree 1993 - 1000 mg po

4 Conclusion

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

5 References

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