Building and evaluation of a PBPK model for Mexiletine in adults

Version	2.0-OSP12.1
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Mexiletine-Model/releases/tag/v2.0
OSP Version	12.1
Qualification Framework Version	3.4

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

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

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1 Introduction

The presented PBPK model of mexiletine has been developed to be used in a PBPK Drug-Drug-Interactions (DDI) network with mexiletine as a substrate and inhibitor of CYP1A2.

Mexiletine is a non-selective voltage-gated sodium channel blocker which belongs to the Class IB anti-arrhythmic group of medicines. It is used to treat arrhythmias within the heart, or seriously irregular heartbeats. The following ADME properties characterize mexiletine pharmacokinetics (Mexiletine Drugs.com, SmPC Namuscla):

Absorption: Mexiletine is well absorbed (~90%) from the gastrointestinal tract. Its first-pass metabolism is low. Peak blood levels are reached in two to three hours.

Distribution: It is 50% to 60% bound to plasma protein, with a volume of distribution of 5 to 7 l/kg.

Metabolism: Mexiletine is mainly metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. With involvement of CYP2D6, there can be either poor or extensive metabolizer phenotypes. The metabolic degradation proceeds via various pathways including aromatic and aliphatic hydroxylation, dealkylation, deamination and N-oxidation. Several of the resulting metabolites are submitted to further conjugation with glucuronic acid (phase II metabolism); among these are the major metabolites p-Hydroxymexiletine, hydroxy-methylMexiletine, and N-hydroxy-Mexiletine.

Elimination: In normal subjects, the plasma elimination half-life of mexiletine is approximately 10 to 12 hours. Approximately 10% is excreted unchanged by the kidney.

After i.v. administration, mexiletine shows linear pharmacokinetics in the dose range 167-200 mg (free base) and healthy volunteers and patients show similar profiles. p.o. data appear dose linear in the range of 83-500 mg as free base. The summary of product characteristics (SPC) for mexiletine (Mexiletine, Drugs.com) reports that absorption rate of mexiletine is reduced in clinical situations such as acute myocardial infarction in which gastric emptying time is increased. For this reason, clinical data from patients after p.o. administration have not been considered during model development.

2 Methods

2.1 Modeling Strategy

The general workflow for building an adult PBPK model has been described by Kuepfer et al. (Kuepfer 2016). Relevant information on the anthropometry (height, weight) was gathered from the respective clinical study, if reported. Information on physiological parameters (e.g. blood flows, organ volumes, hematocrit) in adults was gathered from the literature and has been incorporated in PK-Sim® as described previously (Willmann 2007). 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).

A stepwise approach was used to fit the model to data.

1. Define distribution model, cellular permeability, renal and metabolic clearance on data after single i.v. administration. For this purpose, literature values from Mexiletine, Drugs.com were derived for renal CL and CYP2D6 combined with CYP1A2 metabolic clearance, or total hepatic CL, fitted against the data.

2. Define intestinal permeability and fraction absorbed by fitting the model against data after p.o. single dose administration (Pringle 1986). Investigate multiple oral doses predictions in CYP2D6 extensive and poor metabolizers (Labbé 2000).

The predefined "Standard European Male for DDI" individual (age = 30 y, weight = 73 kg, height = 176 cm, BMI = 23.57 kg/m2) with added CYP2D6 expression obtained from PK-Sim RT PCR database was used if not stated otherwise. For simulations of Japanese subjects (Kusumoto 1998), a typical Japanese individual (age = 30 y, weight = 61.87 kg, height = 168.99 cm, BMI = 21.67 kg/m2) was created in PK-Sim from predefined database "Japanese (2015)" by adding CYP1A2 and CYP2D6 expression from PK-Sim RT PCR database.

For simulations of CYP2D6 PM, the CYP2D6 pathway has been switched off.

Population simulation of single 83 mg p.o. administration was conducted to visually compare the predicted concentration-time profiles to the observed concentrations reported in the literature, in terms of mean and variability. A population of 1000 male individuals was generated based on "Standard European Male for DDI". Age range was limited to 20-40 years.

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 and physico-chemical data

A literature search was performed to collect available information on physico-chemical properties of mexiletine, see Table 1.

Parameter	Unit	Value	Source	Description
MW[+]	g/mol	179.26	DrugBank DB00379	Molecular weight
pK$_{a,base}$[+]		9.2	DrugBank DB00379	Basic dissociation constant
Solubility (pH)[+]	mg/mL	0.54 (7)	DrugBank DB00379	Aqueous Solubility
logD		2.15 - 2.46	DrugBank DB00379	Distribution coefficient
fu[+]	%	50	DrugBank DB00379	Fraction unbound in plasma
CYP1A2 CL	l/h	0.5 - 11	Labbé 2000	Partial metabolic clearance of mexiletine to N-Hydroxymexiletine
CYP2D6 CL	l/h	12 - 13	Labbé 2000	Difference in non-renal CL between CYP2D6 extensive and poor metabolizers
Unspecific liver CL	l/h	12 - 24	Labbé 2000	Non-renal CL – CYP2D6 CL – CYP1A2 CL
Renal elimination[+]	l/h	1.8[+] - 2.1	Labbé 2000	Renal clearance
Ki CYP1A2[+]	µmol/l	0.28	Wei 1991	CYP1A2 inhibition constant

Table 1: Physico-chemical and *in-vitro* metabolization properties of mexiletine extracted from literature. [+]*: Value used in final model*

2.2.2 Clinical data

A literature search was performed to collect available clinical data on mexiletine, see Table 2.

Source	Route	Dose [mg]/ Schedule *	Pop.	Sex	N	Form.	Comment
Campbell 1978[+]	i.v.	200	HV	m	5	solution	
Campbell 1978[+]	p.o.	200	HV	m	5	-	
Begg 1982[+]	p.o.	333.24	HV	m/f	6	tablet	6 IDs
Labbé 2000	p.o.	83.31 b.i.d.	HV	m/f	1	-	EM/PM
Campbell 1978[+]	i.v.	200	patients	-	10	solution	
Pringle 1986[+]	p.o.	83.31 - 166.62 - 249.9 - 333.24 - 499.9	HV	m	12	capsule	
Kusumoto 1998[+]	p.o.	166.62	HV	m	9	capsule	
Pentikäinen 1984[+]	i.v.	166.62	acute myocardial infarction	-	18	solution	acute myocardial infarction
Joeres 1987[+]	p.o.	200	HV	-	1	-	

Table 2: Literature sources of clinical concentration data of mexiletine used for model development and validation. *: single dose unless otherwise specified; EM: extensive metabolizers; PM: poor metabolizers; +: Data used for final parameter identification

2.3 Model Parameters and Assumptions

2.3.1 Absorption

Gastrointestinal permeability was fitted to concentration data after single dose oral administration.

The default dissolution Weibull profile (`Dissolution time (50% dissolved)` = 60min, `Dissolution shape` = 0.92) was used for description of formulation.

2.3.2 Distribution

Physico-chemical parameters were set to the reported values (see Section 2.2.1). It was assumed that the major binding partner in plasma is albumin.

Because mexiletine is a strong base, permeation across the barriers between interstitial space and intracellular space (cellular permeability) had to be adjusted manually, as only uncharged molecules can pass through membranes, which is not accounted for by the permeability calculated by PK-Sim. The parameters `Specific organ permeability` and `Lipophilicity` defining the distribution in tissues were fitted to i.v. data.

After testing the available organ-plasma partition coefficient and cell permeability calculation methods available in PK-Sim, observed clinical data were best described by choosing the partition coefficient calculation by `Rodgers and Rowland` and cellular permeability calculation by `PK-Sim Standard`.

2.3.3 Metabolism and Elimination

Following metabolization and elimination processes are implemented:

- Linear CYP1A2, with specific clearance set to 28.6% of estimated total Liver Plasma Clearance (according to Labbé 2000)
- Linear CYP2D6, with specific clearance set to 37.1% of estimated total Liver Plasma Clearance (according to Labbé 2000)
- Liver plasma clearance, with specific clearance set to 34.3% of estimated total Liver Plasma Clearance (according to Labbé 2000)
- Kidney plasma clearance with plasma clearance value set to reported value (see Section 2.2.1)

The model has been developed with kidney and liver plasma clearances only, without separating between the different enzymes. The parameter `Specific clearance` of the total hepatic clearance was estimated by fitting the model to observed data (see Section 2.2.2). The parameters `Specific clearance` of the linear CYP1A2 and CYP2D6 metabolization processes have been calculated from from the total hepatic clearance by multiplying the identified total hepatic clearance by the reported percentage contribution of the respective enzyme and dividing by the `Reference concentration` of the respective enzyme as given by the PK-Sim database (1.8 μmol/l for CYP1A2 and 0.4 μmol/l for CYP2D6). This is necessary as the `Specific clearance` is multiplied by the concentration of the enzymes in the respective organ, with reference concentration of the dummy enzyme used in the total hepatic clearance being 1 μmol/l per default. With the applied parameter values, CYP1A2 in the liver is responsible for 25% of total mexiletine metabolization, while CYP2D6 in the liver is responsible for 33% of total metabolization. Additional metabolization by CYP2D6 takes place in intestinal mucosa, though to a minor extent.

2.3.4 Automated Parameter Identification

Following parameter values were estimated for the model:

- `Specific clearance` (Total hepatic clearance)
- `Specific organ permeability`
- `Lipophilicity`
- `Plasma clearance` of total Liver Plasma Clearance (divided between three processes in final model)
- `Intestinal permeability (transcellular)`

3 Results and Discussion

The next sections show:

1. Final model input parameters for the building blocks: Section 3.1.
2. 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 parameter values of the final PBPK model are illustrated below.

Compound: Mexiletine

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	0.54 mg/ml	Database-DrugBank DB00379	S_aq	True
Reference pH	7	Database-DrugBank DB00379	S_aq	True
Lipophilicity	2.3770265519 Log Units	Parameter Identification	LogP	True
Fraction unbound (plasma, reference value)	0.5	Database-DrugBank DB00379	fu_plasma	True
Permeability	0.001637391584 cm/min	Parameter Identification	Fit	True
Specific intestinal permeability (transcellular)	0.00047373454608 cm/min	Parameter Identification	Fit	True
Is small molecule	Yes			
Molecular weight	179.26 g/mol	Database-DrugBank DB00379		
Plasma protein binding partner	Albumin			

Calculation methods

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

Processes

Metabolizing Enzyme: CYP1A2-Linear fit

Species: Human

Molecule: CYP1A2

Parameters

Name	Value	Value Origin
Intrinsic clearance	0 l/min	
Specific clearance	0.07944444 1/min	Other-Assumption-28.6% of 0.50 tot hep spec CL - divided by 1.8 µmol/l reference concentration of CYP1A2

Metabolizing Enzyme: CYP2D6-Linear fit

Species: Human

Molecule: CYP2D6

Parameters

Name	Value	Value Origin
Intrinsic clearance	0 l/min	
Specific clearance	0.46375 1/min	Other-Assumption-37.1% of 0.50 tot hep spec CL - divided by 0.4 µmol/l reference concentration of CYP2D6

Systemic Process: Total Hepatic Clearance-Linear fit

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.5	
Lipophilicity (experiment)	2.3770265519 Log Units	
Plasma clearance	0 ml/min/kg	
Specific clearance	0.1715 1/min	Other-Assumption-34.3% of 0.50 tot hep spec CL

Systemic Process: Renal Clearances-CLR - Rmex - Labbe2000

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.5	
Plasma clearance	0 ml/min/kg	
Specific clearance	0.1434490274 1/min	Unknown

Inhibition: CYP1A2-Wei 1991

Molecule: CYP1A2

Parameters

Name	Value	Value Origin
Ki	0.28 µmol/l	Publication-Wei 1991

Formulation: Mexiletine tablet

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	60 min	
Lag time	0 min	
Dissolution shape	0.92	
Use as suspension	Yes	

3.2 Diagnostics Plots

The following section displays the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data listed 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 Mexiletine concentration in plasma

Group	GMFE
Intravenous administration (model building)	1.19
Oral administration (model building)	1.32
Oral administration (model validation)	1.24
All	1.28
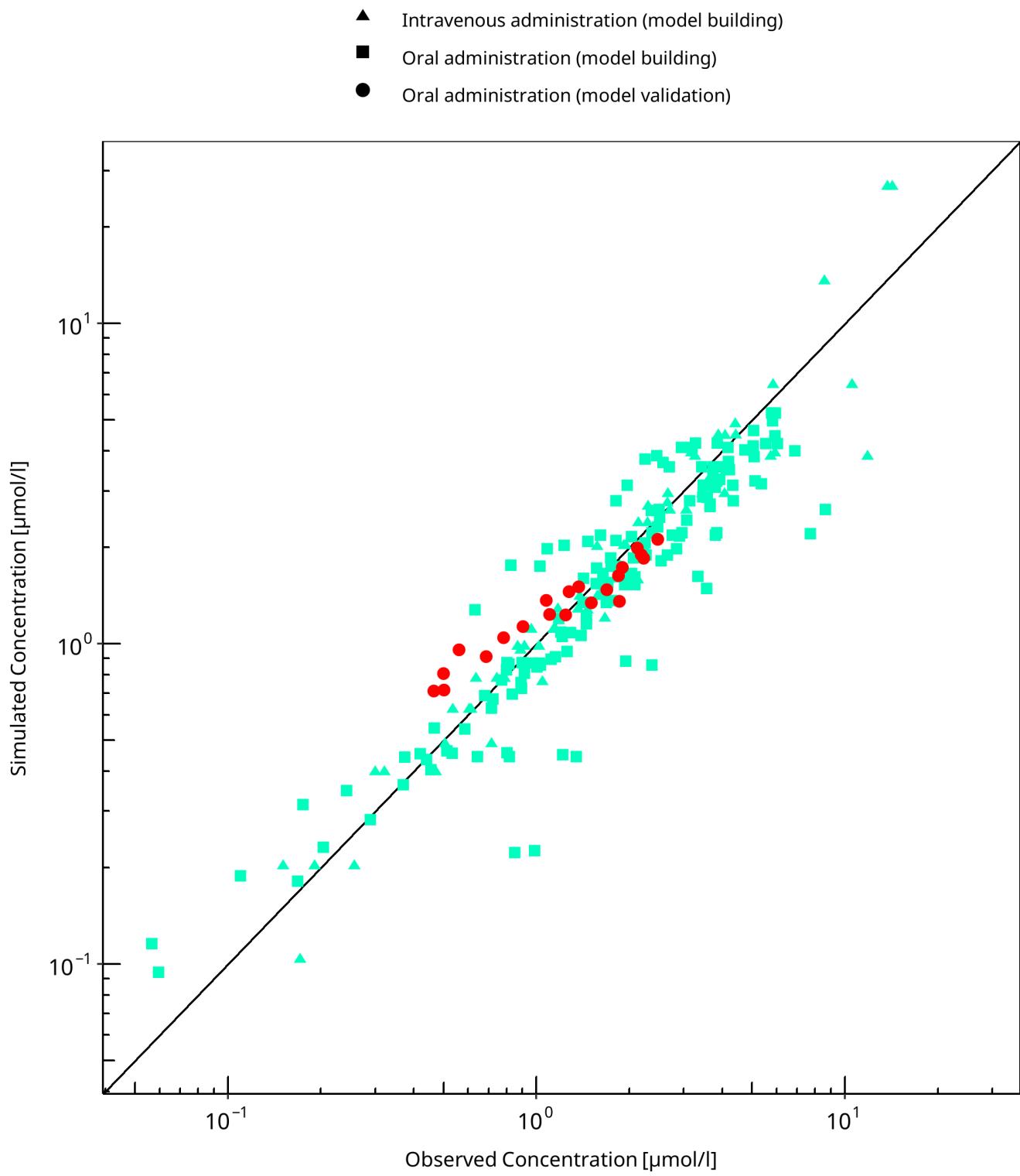
Figure 3-1: Mexiletine concentration in plasma
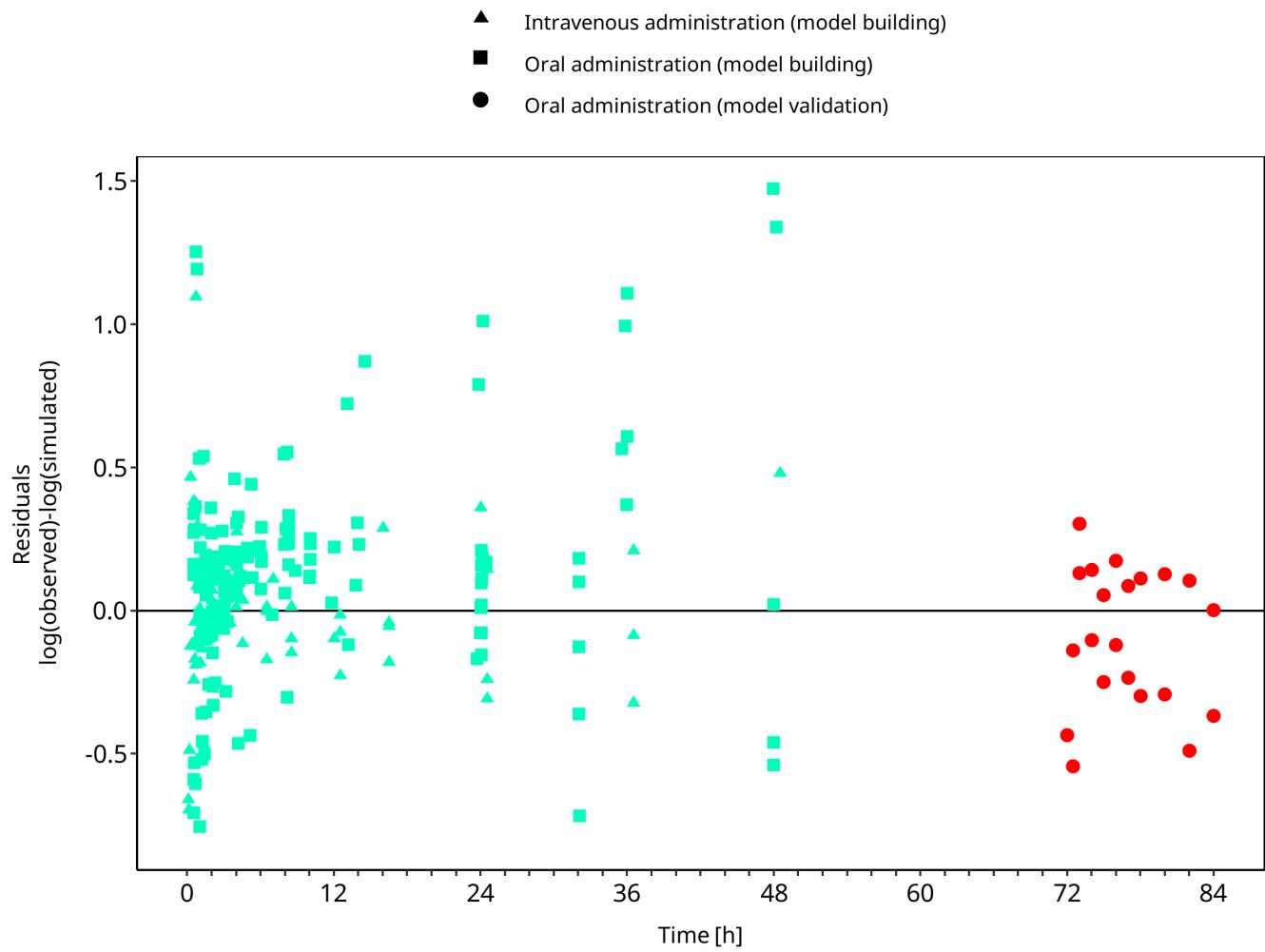
Figure 3-2: Mexiletine concentration in plasma

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
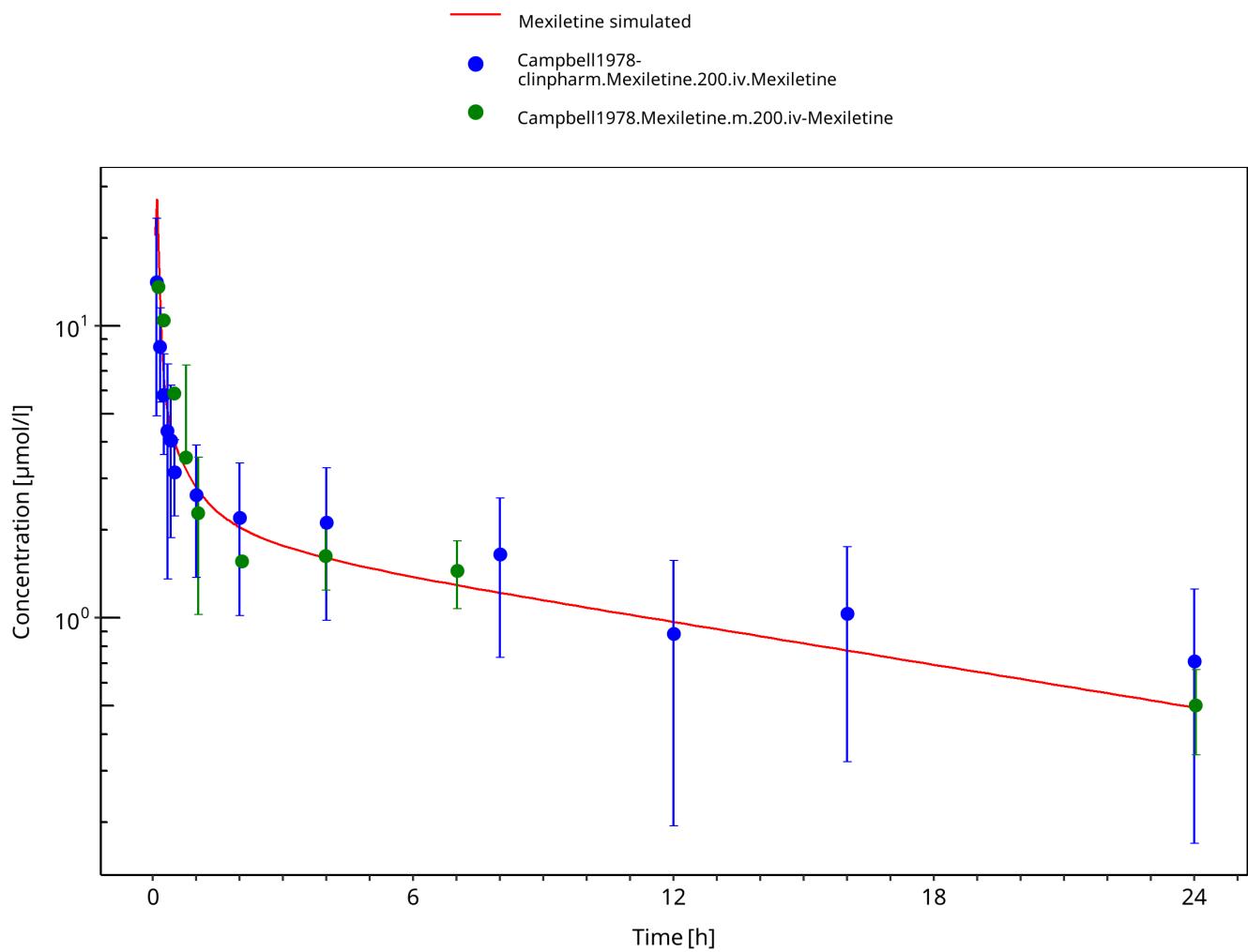
Figure 3-3: Mexiletine 200 mg iv
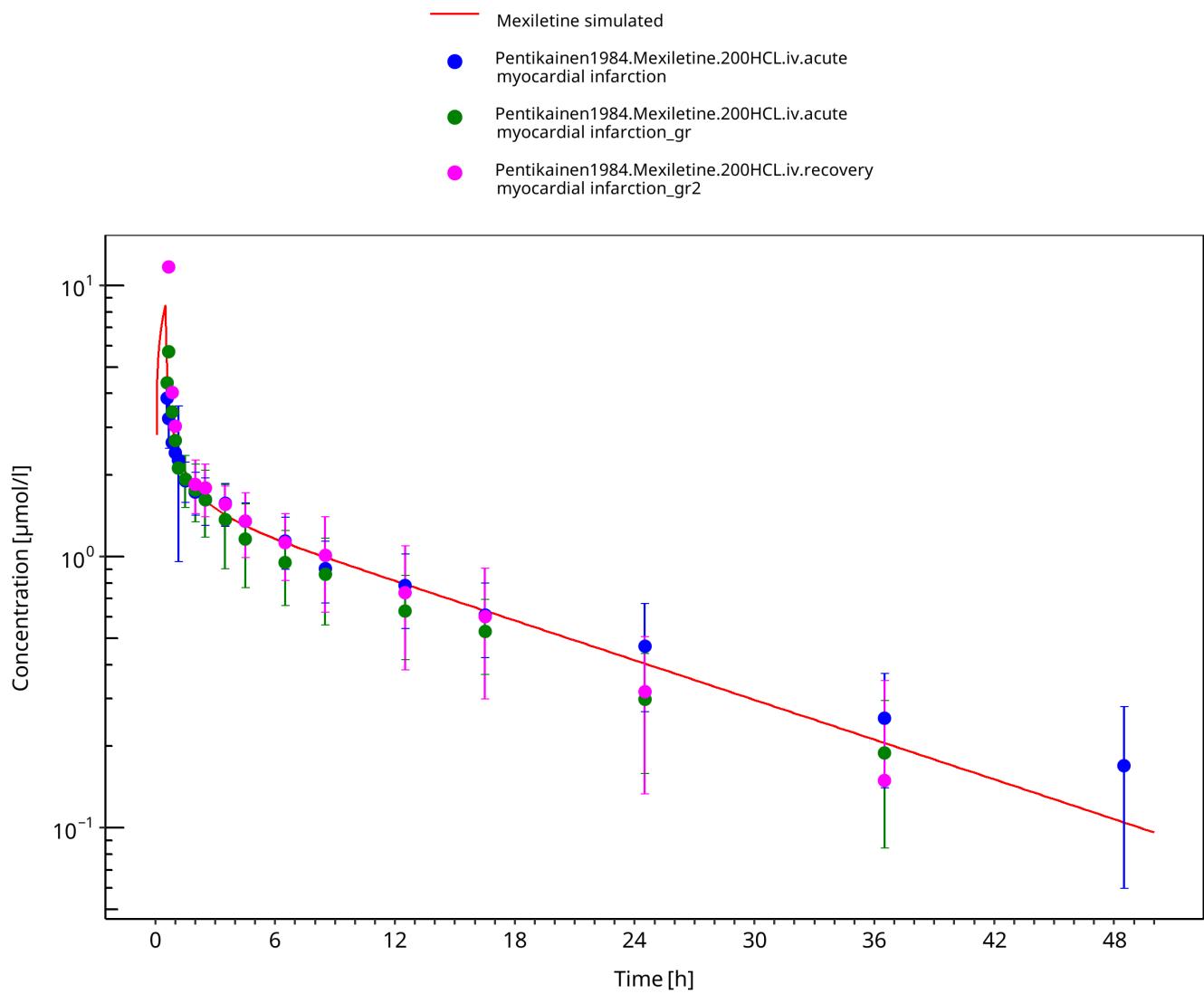
Figure 3-4: Mexiletine 200 mg iv 30 min
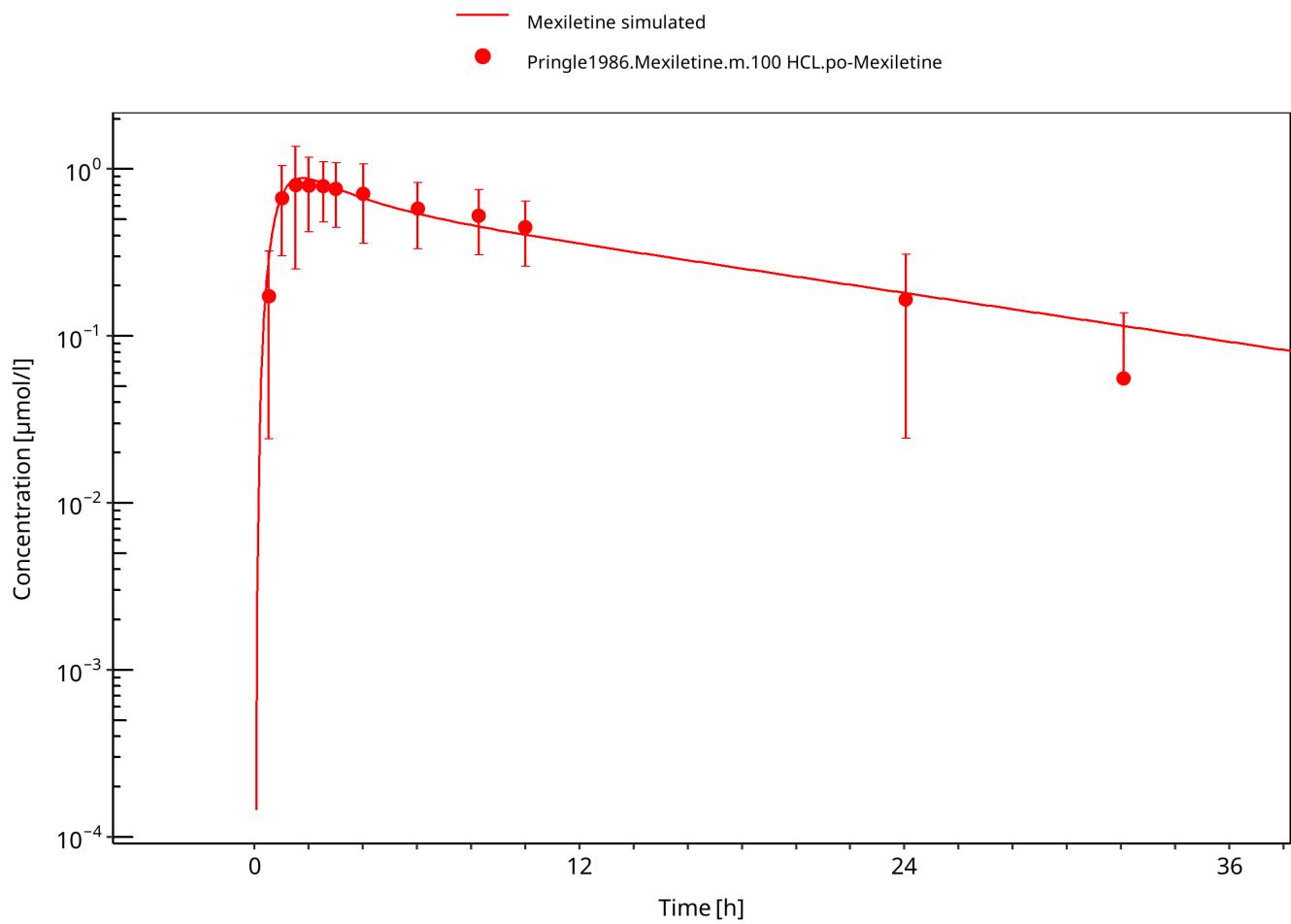
Figure 3-5: Mexiletine HCL 100 mg po
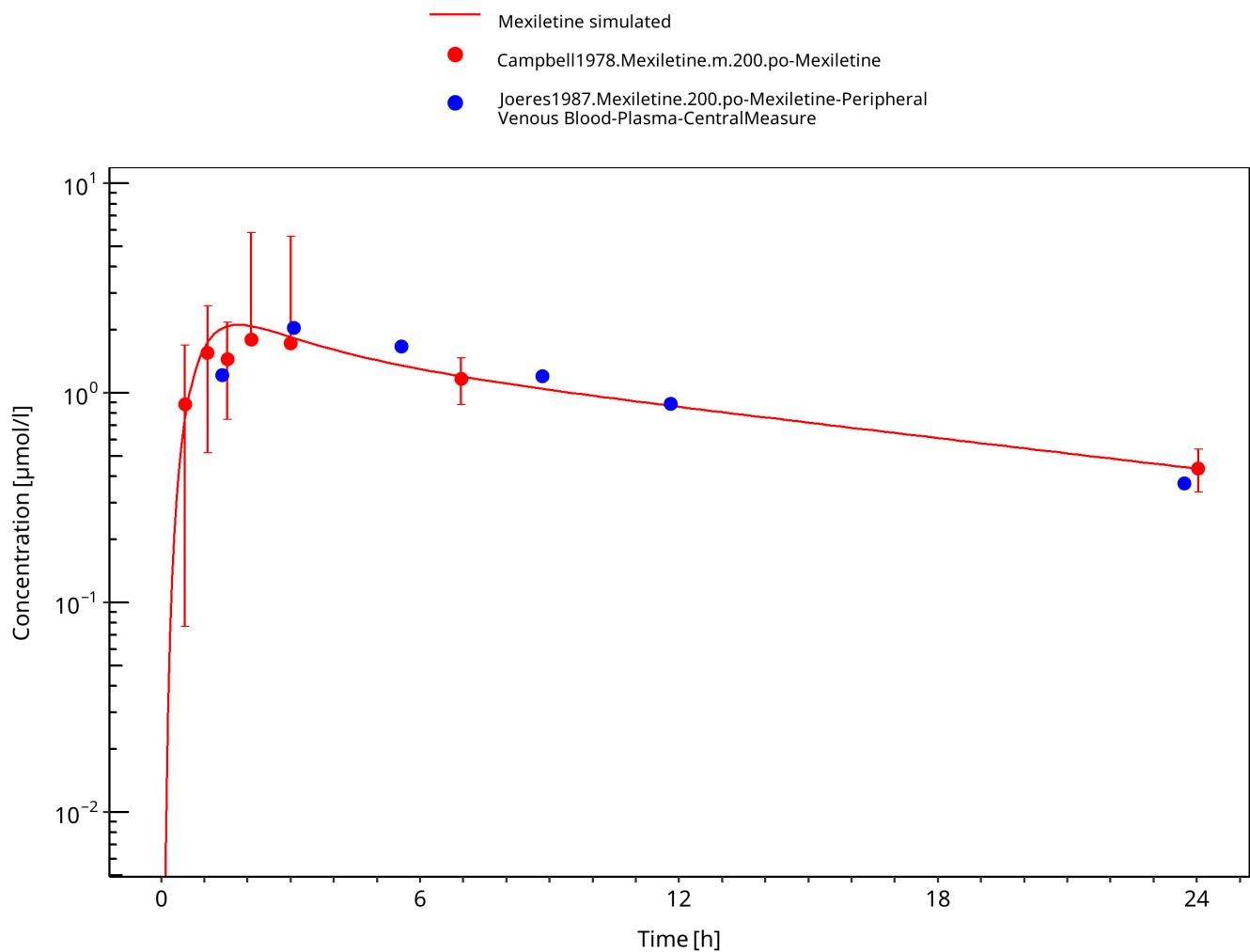
Figure 3-6: Mexiletine 200 mg po
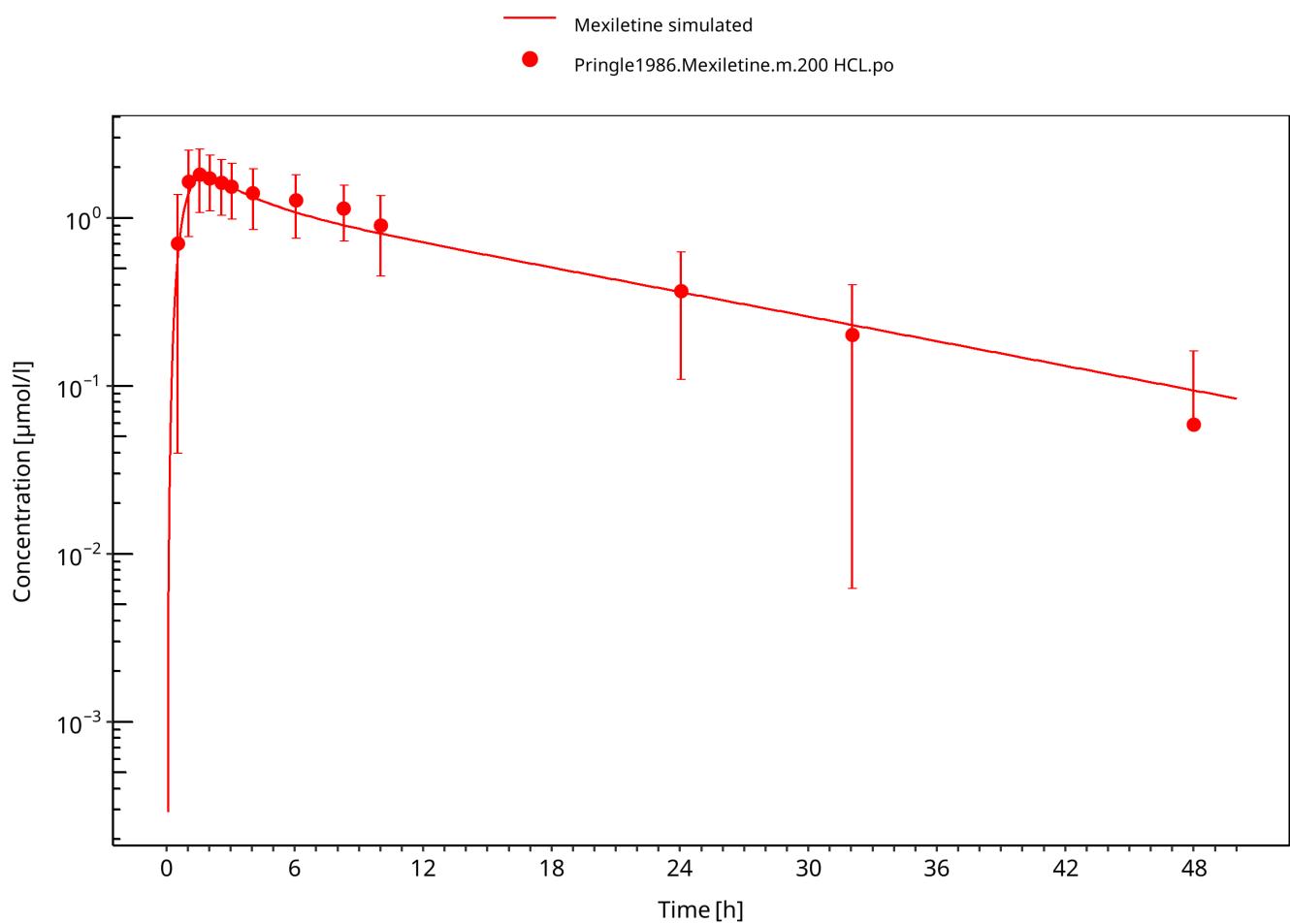
Figure 3-7: Mexiletine HCL 200 mg po
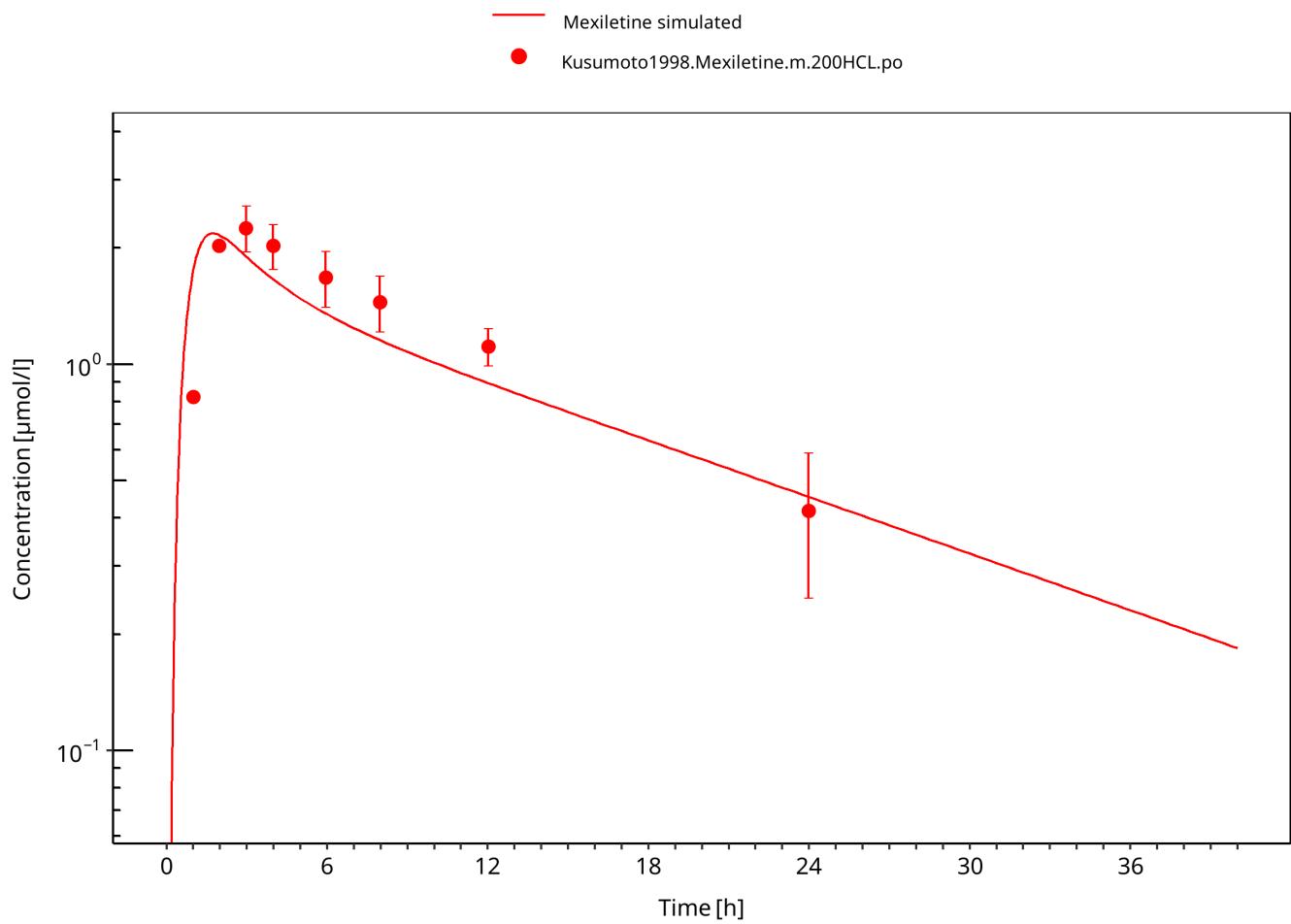
**Figure 3-8: Mexiletine HCL 200 mg po asian**
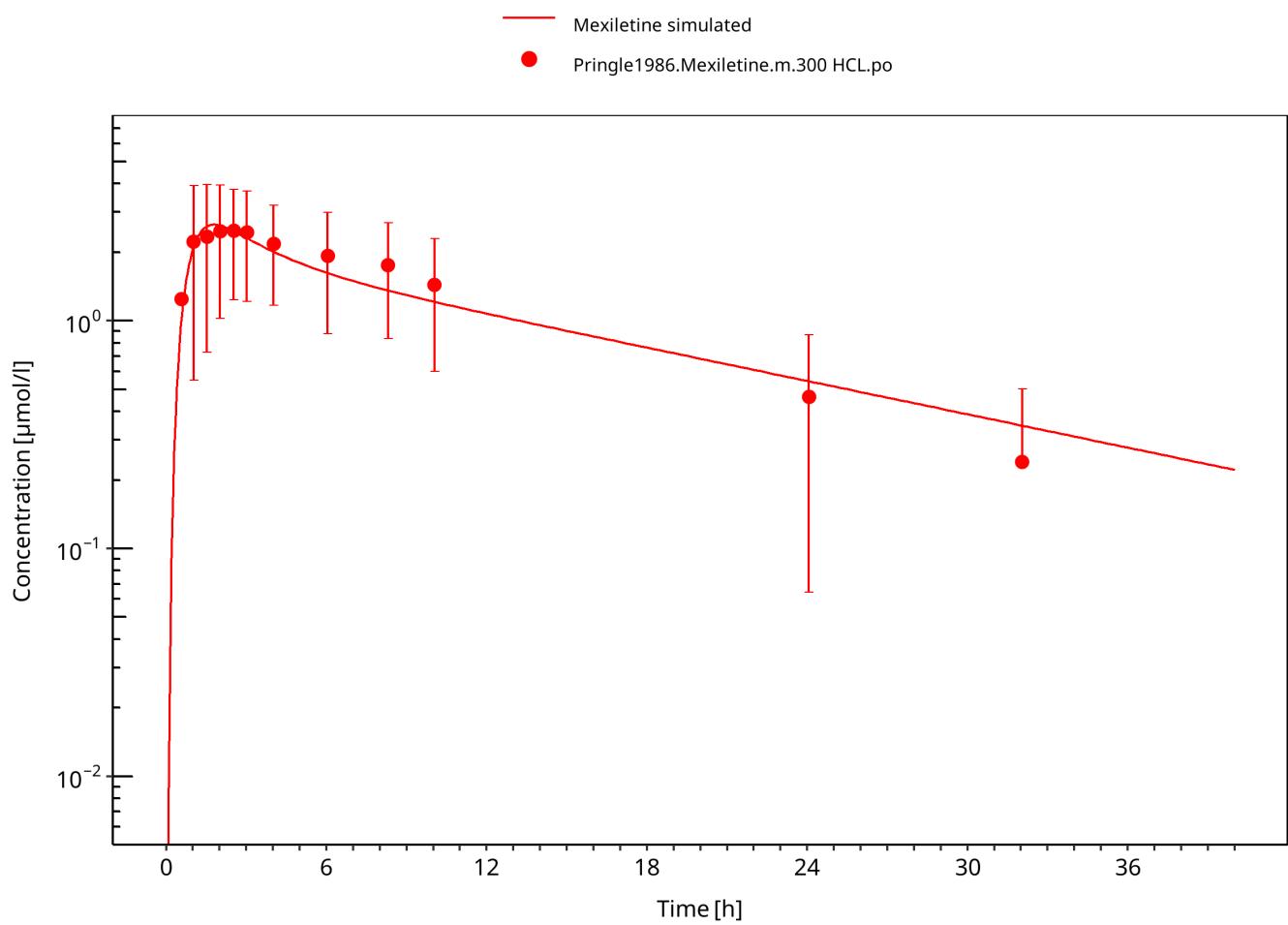
**Figure 3-9: Mexiletine HCL 300 mg po**
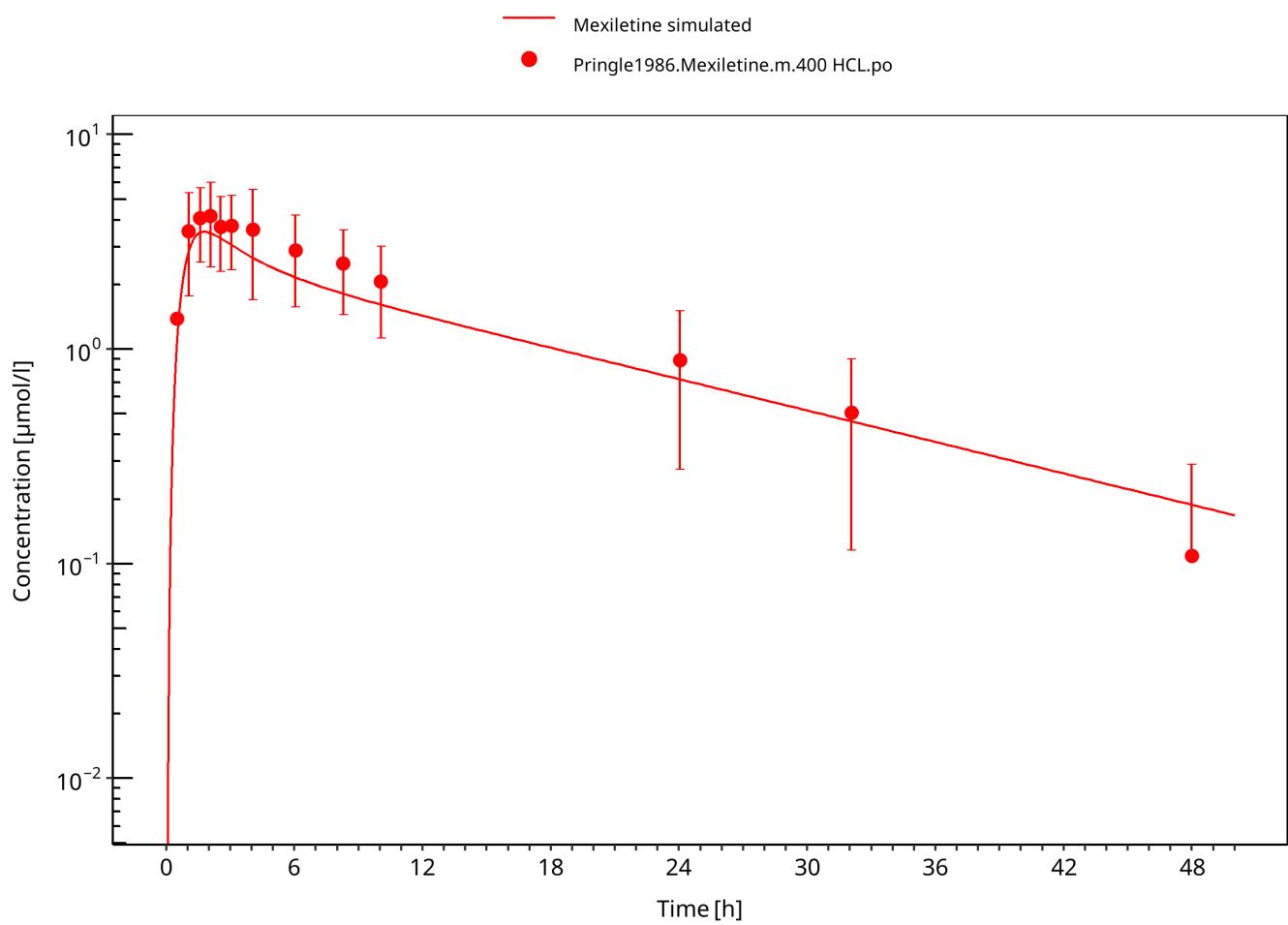
**Figure 3-10: Mexiletine HCL 400 mg po**
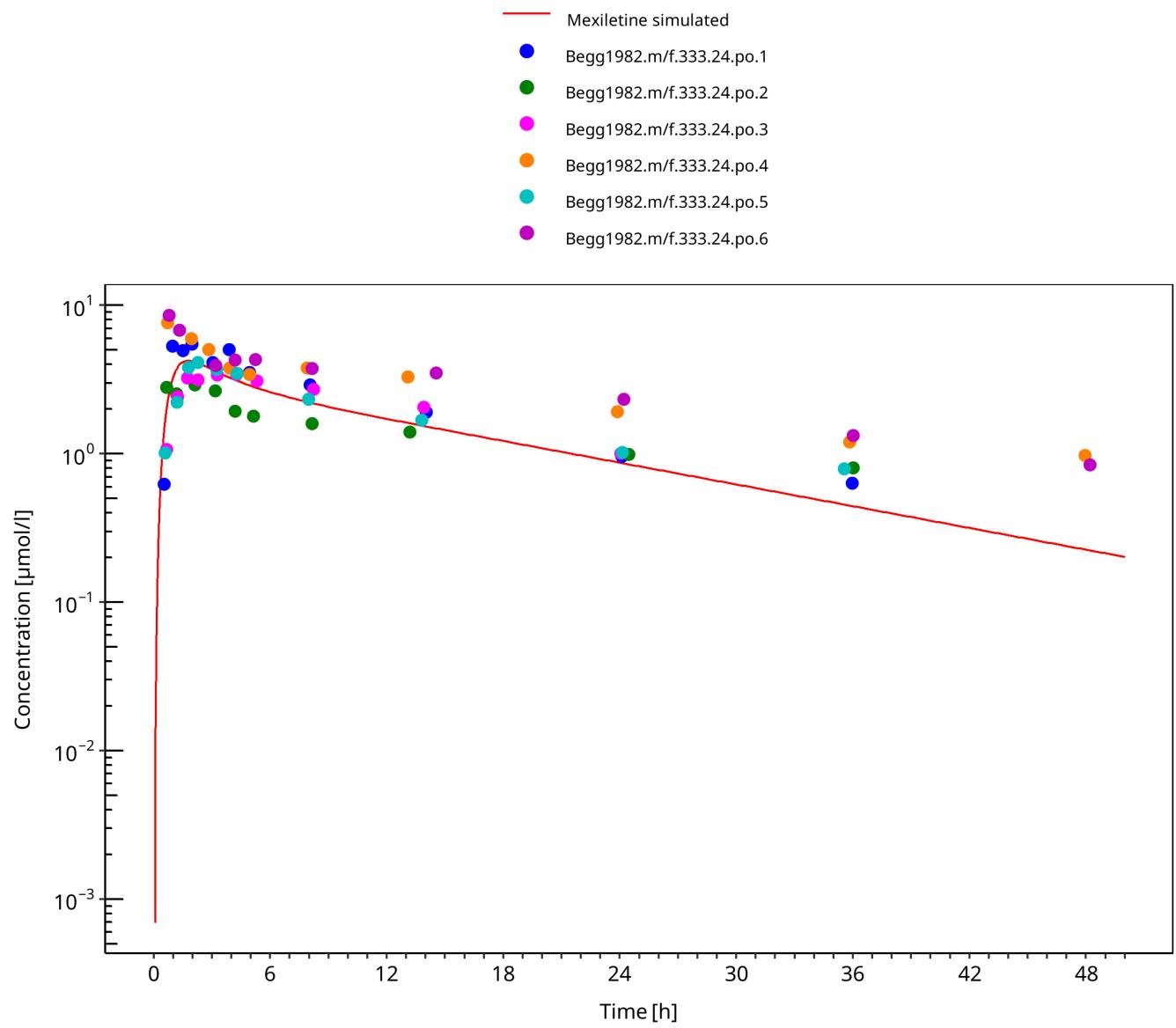
Figure 3-11: Mexiletine 400 mg po
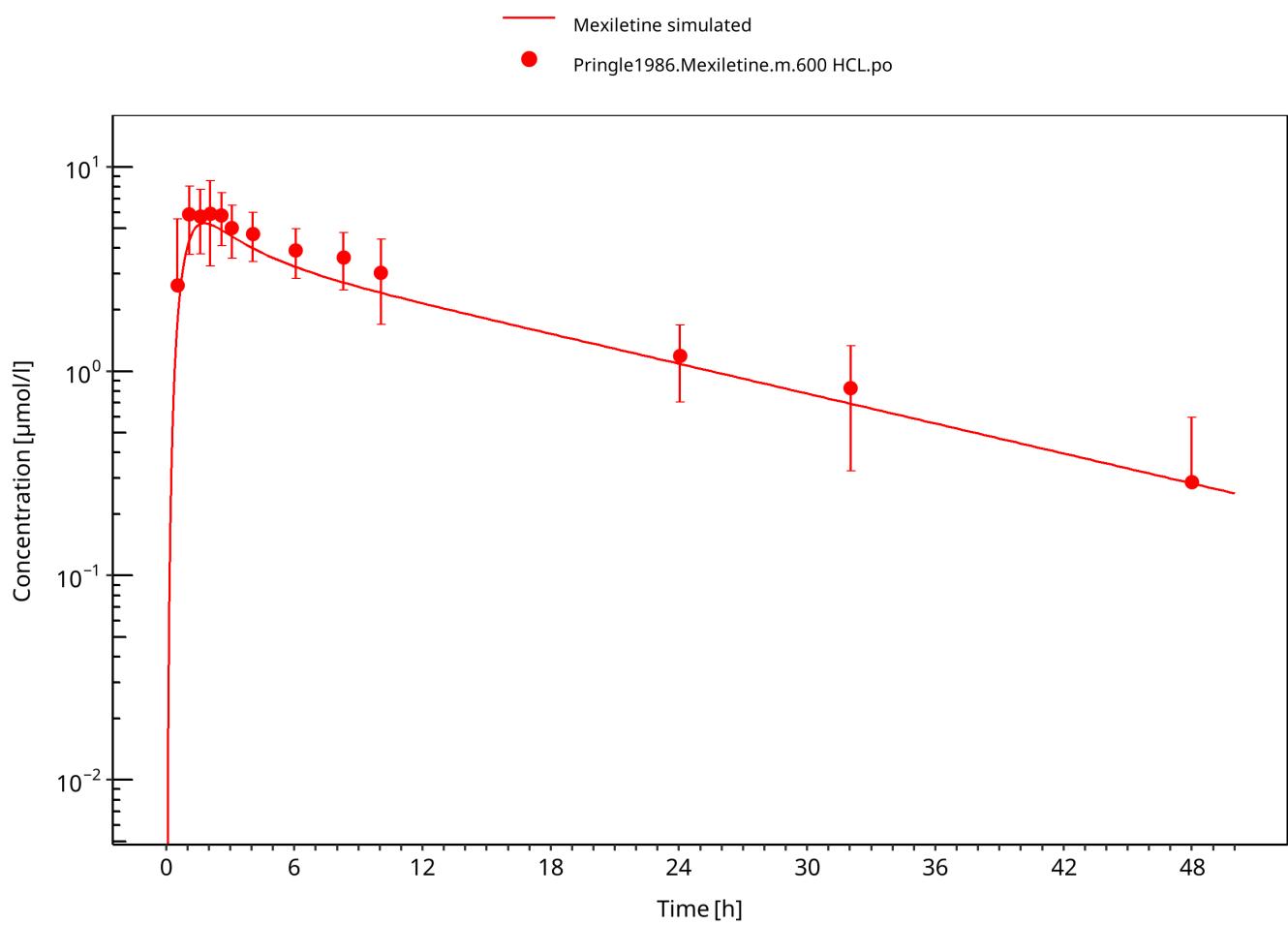
Figure 3-12: Mexiletine HCL 600 mg po

3.3.2 Model Verification
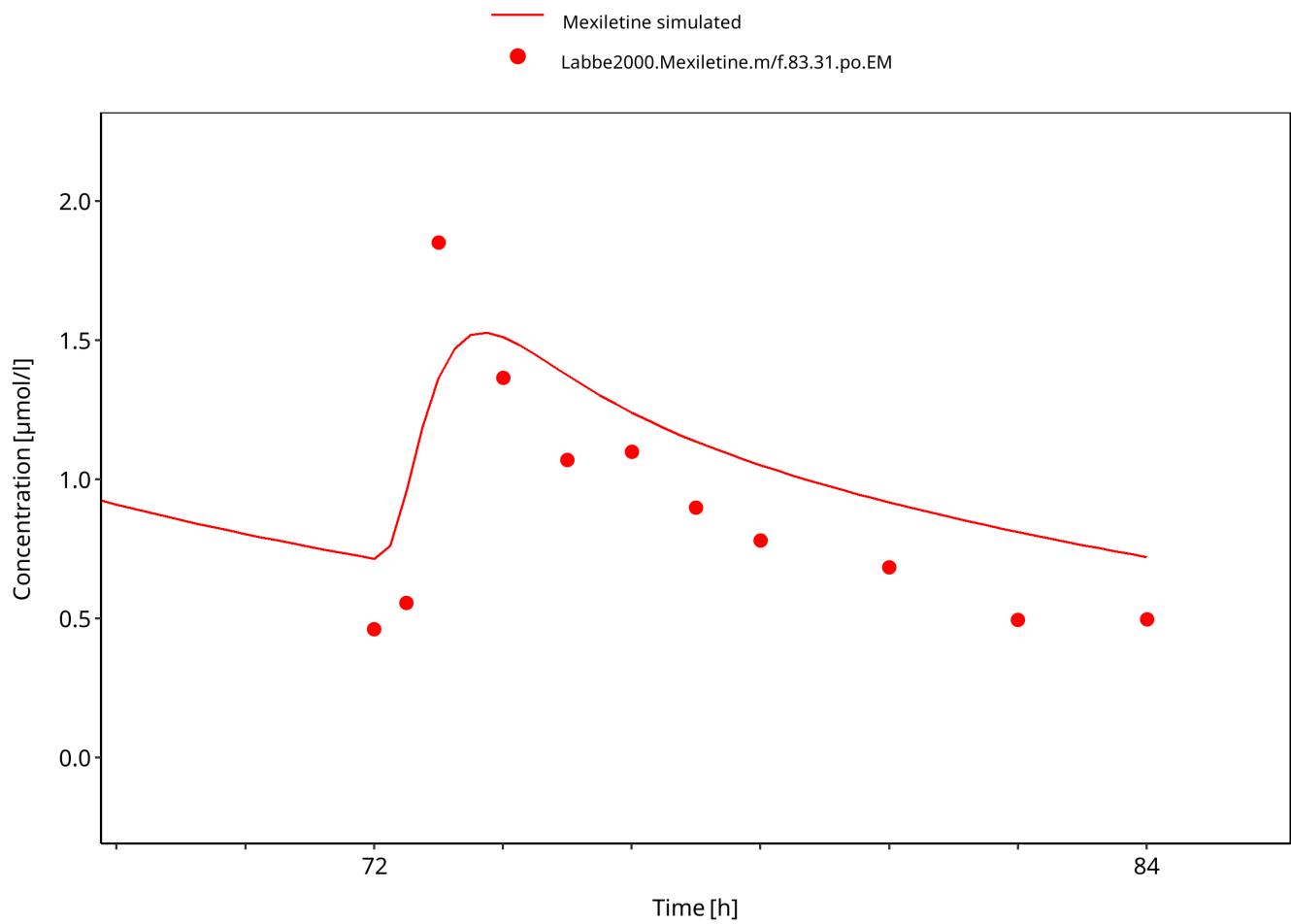
Figure 3-13: Mexiletine 83.31 mg po bid EM
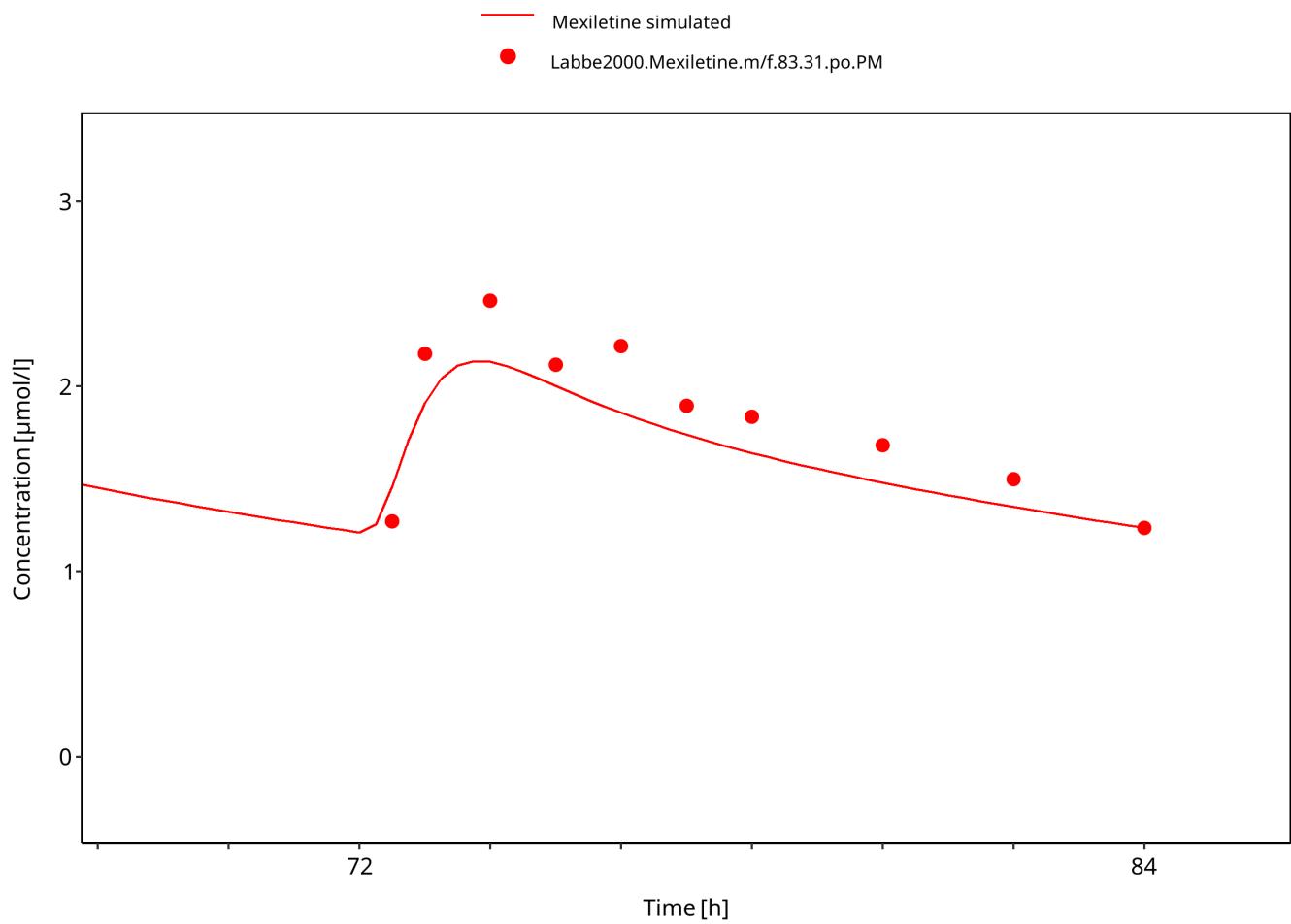
Figure 3-14: Mexiletine 83.31 mg po bid PM

Legend:
- Mexiletine simulated-Median
- Mexiletine simulated-Range 2.5 to 97.5%
- Pringle1986.Mexiletine.m.100 HCL.po-Mexiletine-Peripheral Venous Blood-Plasma-CentralMeasure
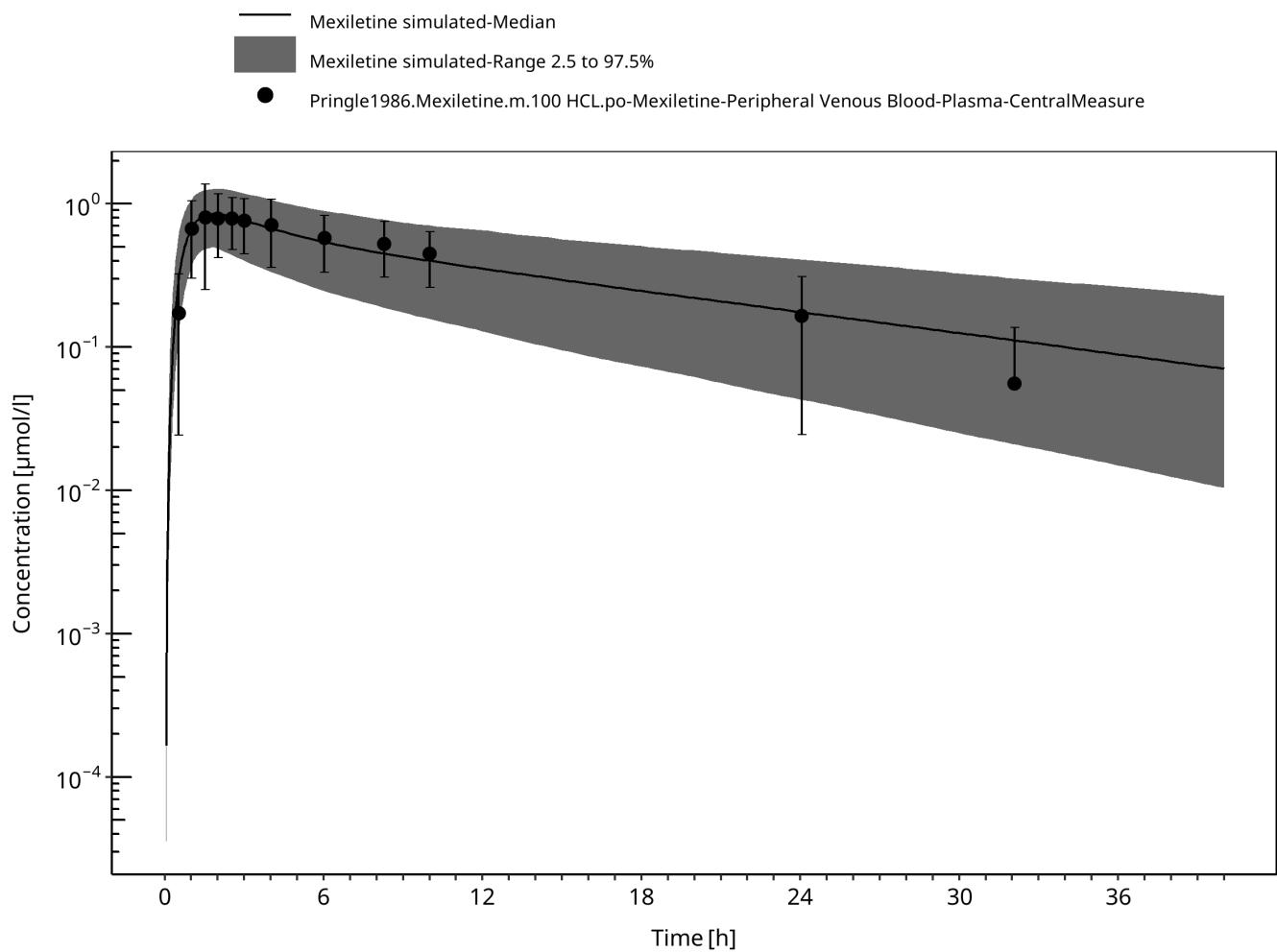
Figure 3-15: Time Profile Analysis

4 Conclusion

The PBPK model developed for mexiletine was able to accurately predict the time-profiles following i.v. and p.o. dosing of mexiletine in EM and PM phenotypes. Observed variability was generally larger than the predicted in population simulations. Depending on study population, smoking status or variation in CYP-phenotypes may lead to additional variability which might be not included in the PK-Sim ontogeny factor.

The predicted fraction excreted in urine was similar to the fraction reported in the label (9% vs 10%). The predicted bioavailability was 85%, compared to the observed as per label of 90%.

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6 Glossary

ADME	Absorption, Distribution, Metabolism, Excretion
AUC	Area under the plasma concentration versus time curve
AUCinf	AUC until infinity
AUClast	AUC until last measurable sample
AUCR	Area under the plasma concentration versus time curve Ratio
b.i.d.	Twice daily (bis in diem)
CL	Clearance
Clint	Intrinsic liver clearance
Cmax	Maximum concentration
CmaxR	Maximum concentration Ratio
CYP	Cytochrome P450 oxidase
CYP1A2	Cytochrome P450 1A2 oxidase
CYP2C19	Cytochrome P450 2C19 oxidase
CYP3A4	Cytochrome P450 3A4 oxidase
DDI	Drug-drug interaction
e.c.	Enteric coated
EE	Ethinylestradiol
EM	Extensive metabolizers
fm	Fraction metabolized
FMO	Flavin-containing monooxygenase
fu	Fraction unbound
FDA	Food and Drug administration
GFR	Glomerular filtration rate
HLM	Human liver microsomes
hm	homozygous
ht	heterozygous
IM	Intermediate metabolizers

ADME	Absorption, Distribution, Metabolism, Excretion
i.v.	Intravenous
IVIVE	In Vitro to In Vivo Extrapolation
Ka	Absorption rate constant
kcat	Catalyst rate constant
Ki	Inhibitor constant
Kinact	Rate of enzyme inactivation
Km	Michaelis Menten constant
m.d.	Multiple dose
OSP	Open Systems Pharmacology
PBPK	Physiologically-based pharmacokinetics
PK	Pharmacokinetics
PI	Parameter identification
PM	Poor metabolizers
RT-PCR	Reverse transcription polymerase chain reaction
p.o.	Per os
q.d.	Once daily (quaque diem)
SD	Single Dose
SE	Standard error
s.d.SPC	Single dose Summary of Product Characteristics
SD	Standard deviation
TDI	Time dependent inhibition
t.i.d	Three times a day (ter in die)
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UM	Ultra-rapid metabolizers