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

Version	**master-OSP12.1**
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Lisinopril-Model/releases/tag/vmaster
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/

Table of Contents

1 Introduction

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

Lisinopril is an oral, long-acting angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension and heart failure. It reduces blood pressure by inhibiting the conversion of angiotensin I to angiotensin II, leading to vasodilation and decreased aldosterone secretion. Unlike many ACE inhibitors, lisinopril is a hydrophilic compound that does not undergo hepatic metabolism and is excreted unchanged in the urine. Its absorption is moderate, with approximately 25% of the administered dose reaching systemic circulation, and peak plasma concentrations occurring 6-8 hours after oral administration. Food intake does not significantly affect its absorption.

Lisinopril follows a biphasic pharmacokinetic profile, with an initial distribution phase and a prolonged terminal phase, which reflects its strong binding to ACE rather than drug accumulation. Its elimination occurs primarily through renal excretion, with a consistent clearance profile across different doses. The drug has an effective accumulation half-life of approximately 12 hours, supporting once-daily dosing for sustained blood pressure control.

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

The presented Lisinopril PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (https://github.com/Open-Systems-Pharmacology/Lisinopril-model).

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. (Kuepfer 2016) The relevant 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 (PK-Sim Ontogeny Database Version 7.3). 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 (Schlender 2016) or otherwise referenced for the specific process.

First, a base mean model was built using clinical Phase I data including selected single dose studies with intravenous and oral applications of lisinopril to find an appropriate structure to describe the pharmacokinetics in plasma. The mean PBPK model was developed using a typical European individual.

Unknown parameters 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.

Once the appropriate structural model was identified, additional parameters for tablet formulations were identified.

The model was then verified by simulating:

- Oral administration of lisinopril in fasted state
- Oral administration of lisinopril in fed state

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 lisinopril. The obtained information from literature is summarized in the table below.

Parameter	Unit	Value	Source	Description
MW	g/mol	405.49	PubChem 2024	Molecular weight
pK_a	-	1.63 (strongest acidic)	Takács-Novák 2003	Acid dissociation constant
pK_a	-	10.75 (strongest basic)	Takács-Novák 2003	Acid dissociation constant
Solubility (pH)	1 at pH7.2	mg/mL	Cayman Chem 2022	Aqueous Solubility, FaSSIF, ...
fu	%	100	DrugBank 2025	Fraction unbound in plasma

2.2.2 Clinical Data

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

2.2.2.1 Model Building

The following studies were used for model building (training data):

Dose [mg]	Dosing	PK data	Dataset	Reference
2.64	iv, sd	plasma	training	Beermann 1989
5.28	iv, sd	plasma	training	Beermann 1989
10.56	iv, sd	plasma	training	Beermann 1989
20	po, tab, fasted, qd	plasma	training	Beermann 1989

iv = intravenous; po = oral administration; tab = tablet administration; sd = single dose; qd = once daily

2.2.2.2 Model Verification

The following studies were used for model verification:

Dose [mg]	Dosing	PK data	Dataset	Reference
10	po, tab, fasted, sd	plasma	training	Ulm 1982
5	po, tab, fasted, qd	plasma	training	Gautam 1987
20	po, tab, fasted, sd	plasma	training	Mojaverian 1986
20	po, tab, fed, sd	plasma	training	Mojaverian 1986

iv = intravenous; po = oral administration; tab = tablet administration; sd = single dose; qd = once daily

2.3 Model Parameters and Assumptions

2.3.1 Absorption

The parameters values for `Intestinal permeability` and `Permeability P(intracellular->interstitial) Mucosa` were optimized based on clinical oral data, see Section 2.3.4. The measured solubility of lisinopril was taken from Product information from Cayman Chemical Co (see Section 2.2.1).

Tablet dissolution was modeled using an empirical Weibull dissolution approach, with the corresponding parameters estimated (Dissolution time and shape).

2.3.2 Distribution

Lisinopril does not bind to plasma proteins (fu = 100 %) (see Section 2.2.1) (Beermann 1989). In this PBPK model, a value of 100% was assigned to `Fraction unbound (plasma, reference value)`.

An important parameter influencing the resulting volume of distribution is lipophilicity, which was also estimated.

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 `Schmitt` and cellular permeability calculation by `Charged dependent Schmitt`.

2.3.3 Metabolism and Elimination

After absorption, Lisinopril remains unbound to plasma proteins, does not undergo metabolism, and is not secreted into bile. The drug is primarily eliminated through renal plasma clearance, with `Plasma Clearance` estimated accordingly.

2.3.4 Automated Parameter Identification

This is the result of the final parameter identification.

Model Parameter	Optimized Value	Unit
`lipophilicity`	-0.58	Log Units
`Plasma Clearance (Renal clearance)`	1.18	
`Intestinal permeability`	1.35E-8	cm/s
`Weibull Dissolution time`	120	min
`Weibull Dissolution shape`	3.00	-
`Permeability P(intracellular->interstitial) Mucosa (large intestine)`	8.1132E-6	cm/min
`Permeability P(intracellular->interstitial) Mucosa (small intestine)`	3E-09	cm/min

3 Results and Discussion

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

The model was evaluated covering data from studies including in particular

- Intravenous Bolus
- Oral administration over fed and fasted states.

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: Lisinopril

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	1000 mg/l		Measurement	True
Reference pH	7.2		Measurement	True
Lipophilicity	-0.5781319594 Log Units	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2025-01-23 23:53	Measurement	True
Fraction unbound (plasma, reference value)	1		Measurement	True
Is small molecule	Yes			
Molecular weight	405.5 g/mol			
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	Schmitt
Cellular permeabilities	Charge dependent Schmitt

Processes

Systemic Process: Renal Clearances-Renal Clearance

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	1	
Plasma clearance	1.18 ml/min/kg	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2025-01-23 23:53

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 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
Lisinopril Intravenous Administration (model building)	1.46
Lisinopril Oral Administration (model building)	1.31
Lisinopril Oral Administration (model verification)	1.84
All	1.56

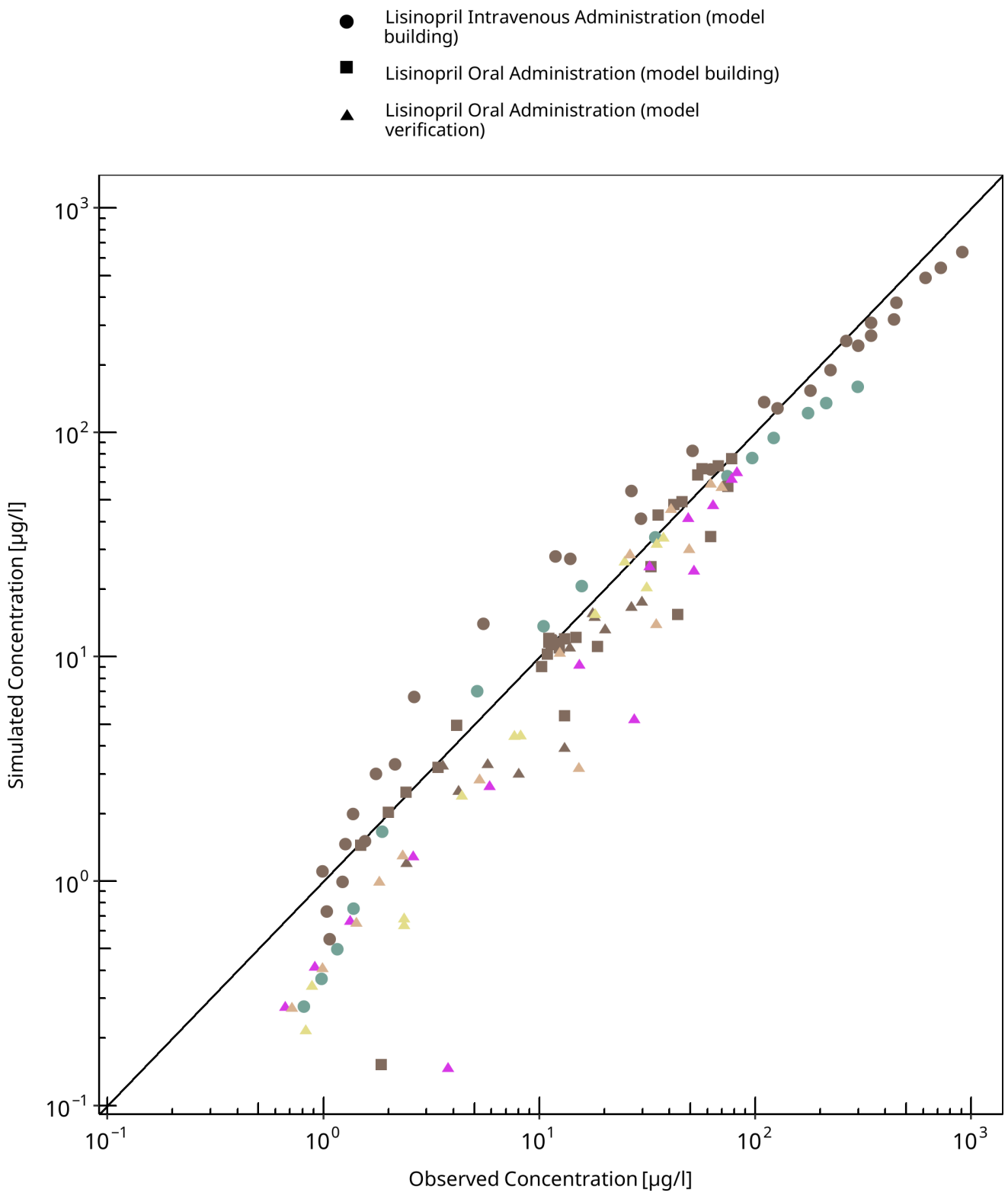

Figure 3-1: Goodness of fit plot for concentration in plasma

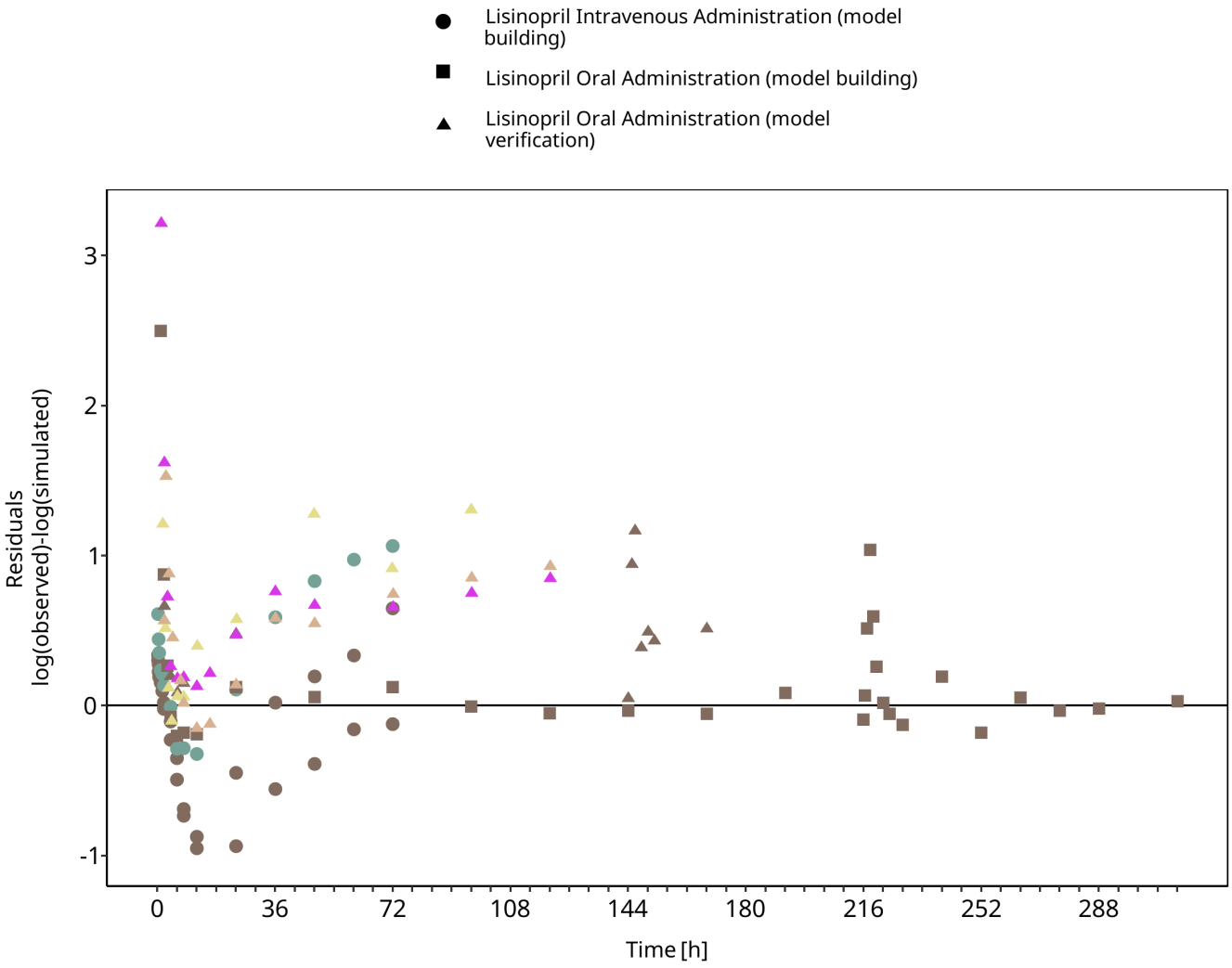

Figure 3-2: Goodness of fit plot for concentration in plasma

3.3 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in Section 2.2.2 are presented below.

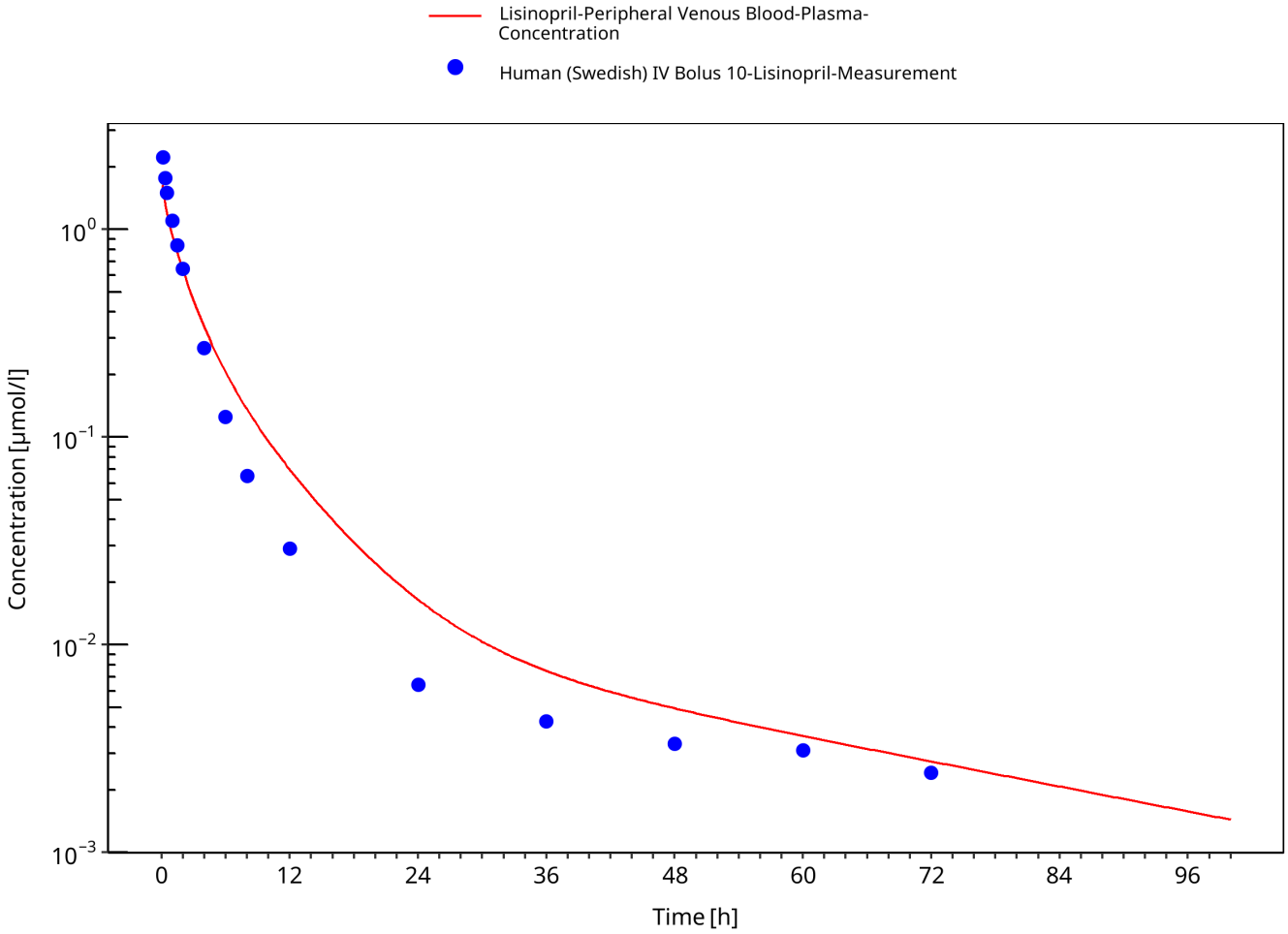

Figure 3-3: Lisinopril - IV, Beermann Bolus 10.56mg

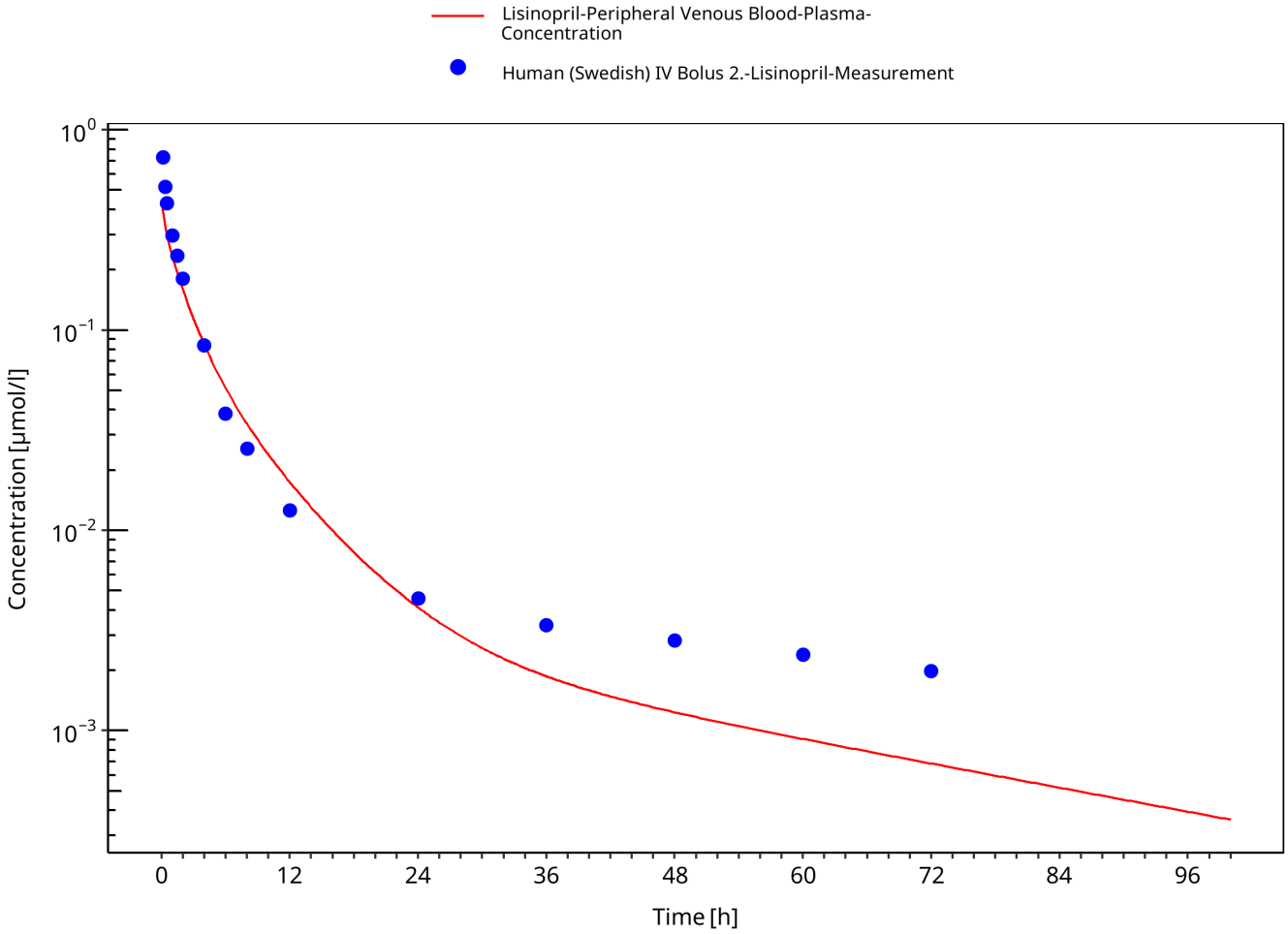

Figure 3-4: Lisinopril - IV, Beermann Bolus 2.24mg

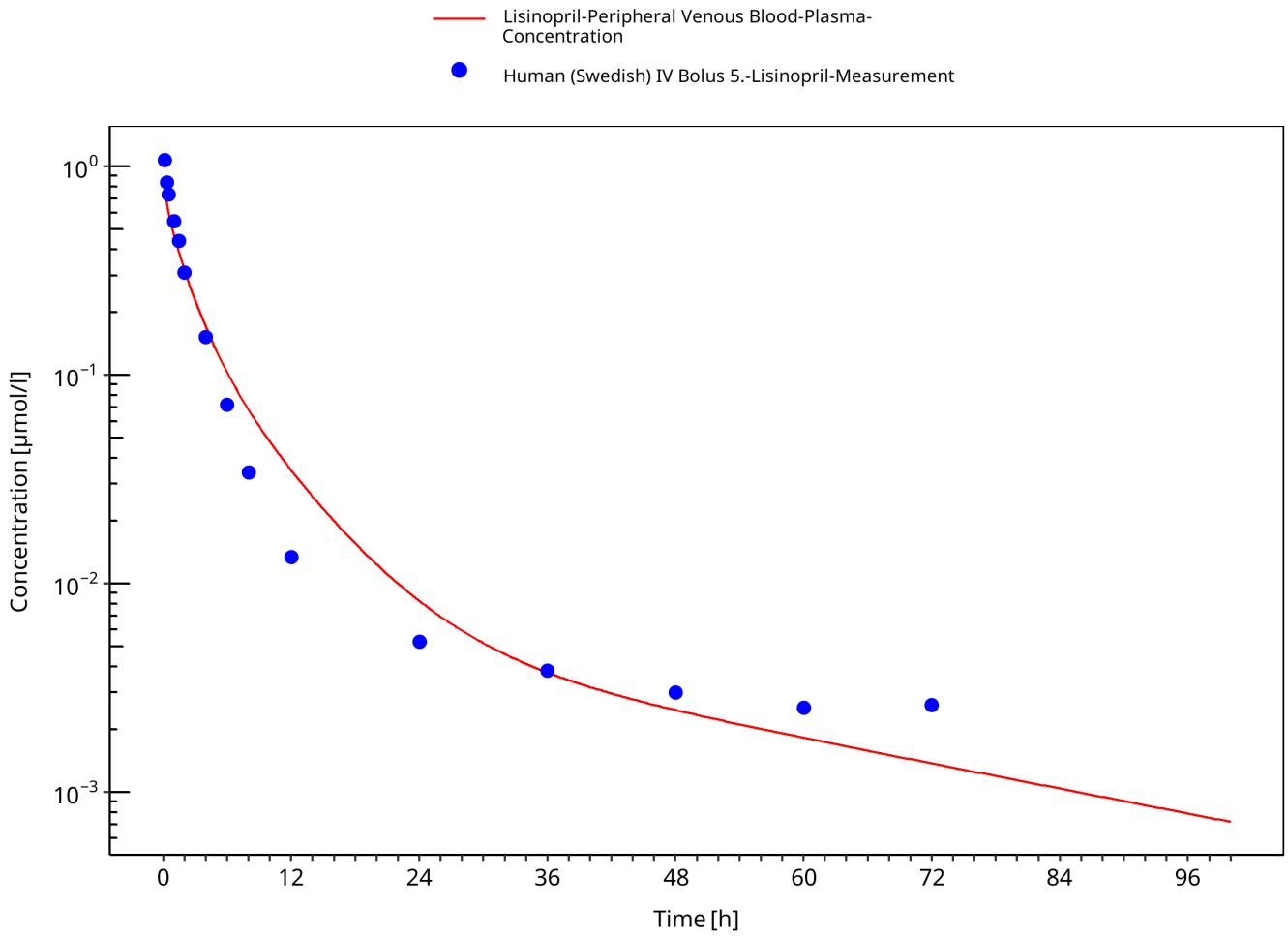

Figure 3-5: Lisinopril - IV, Beermann Bolus 5.28mg

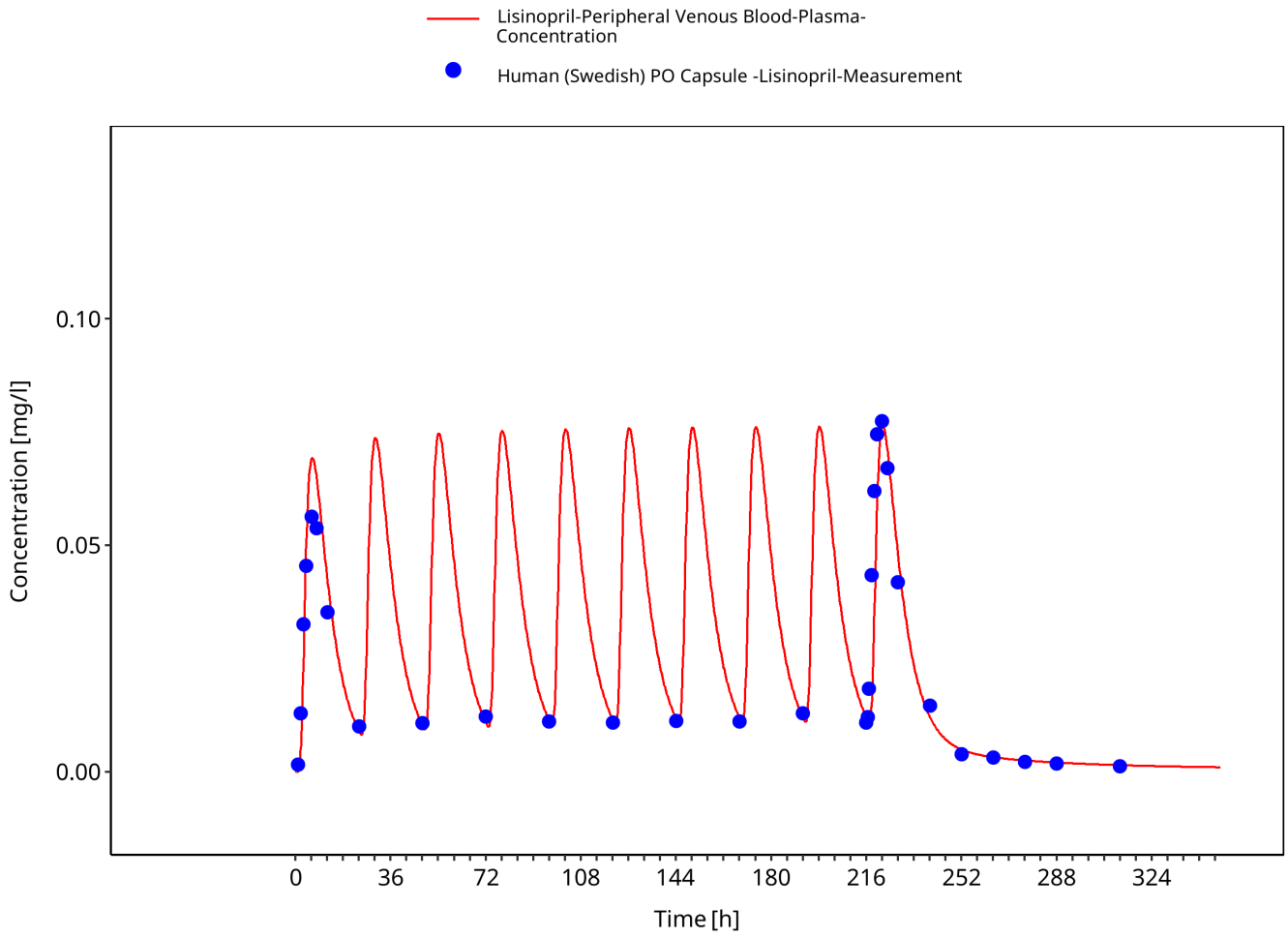

Figure 3-6: Lisinopril - PO, Beermann repeated 20mg

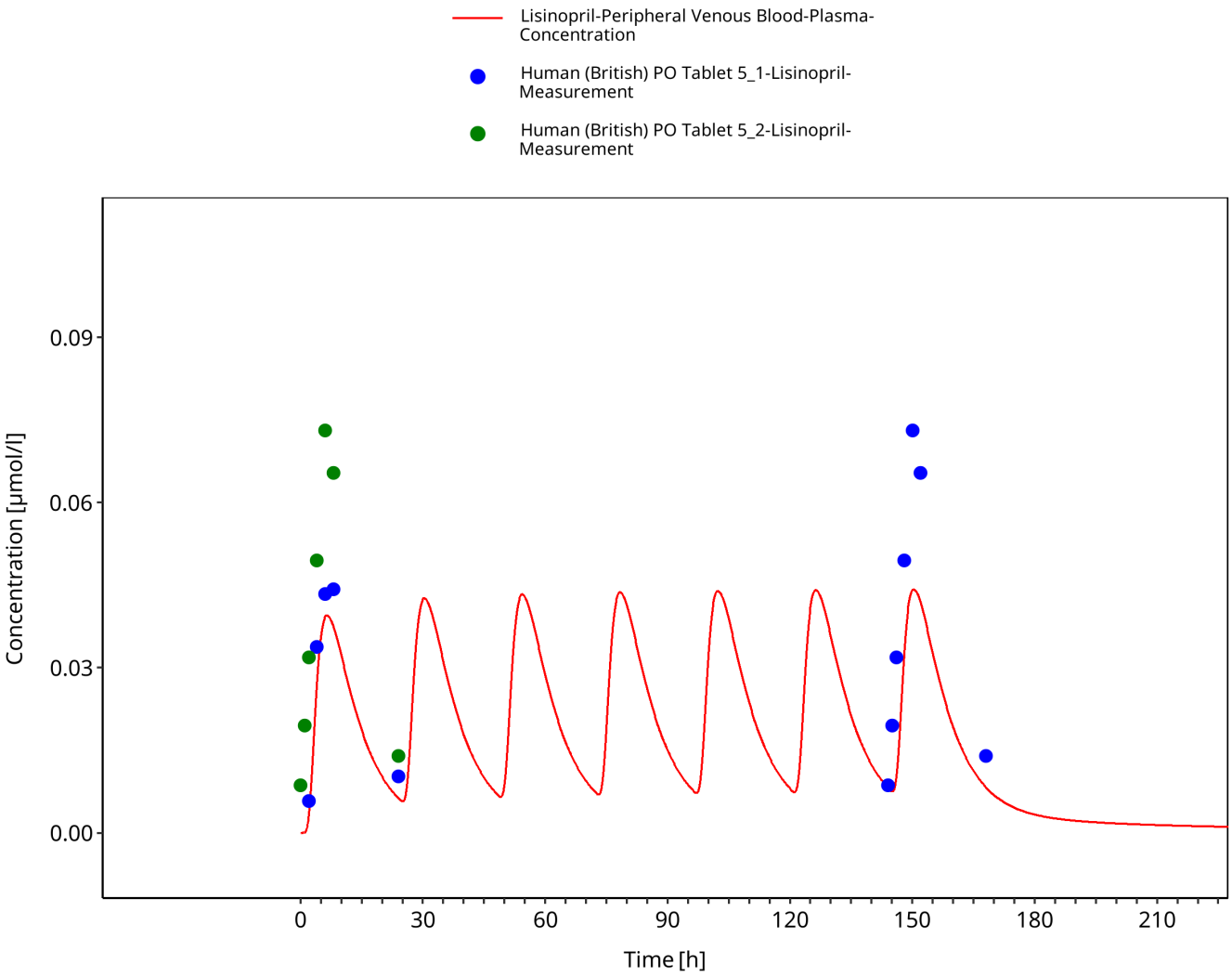

Figure 3-7: Lisinopril - PO, Gautam 5mg

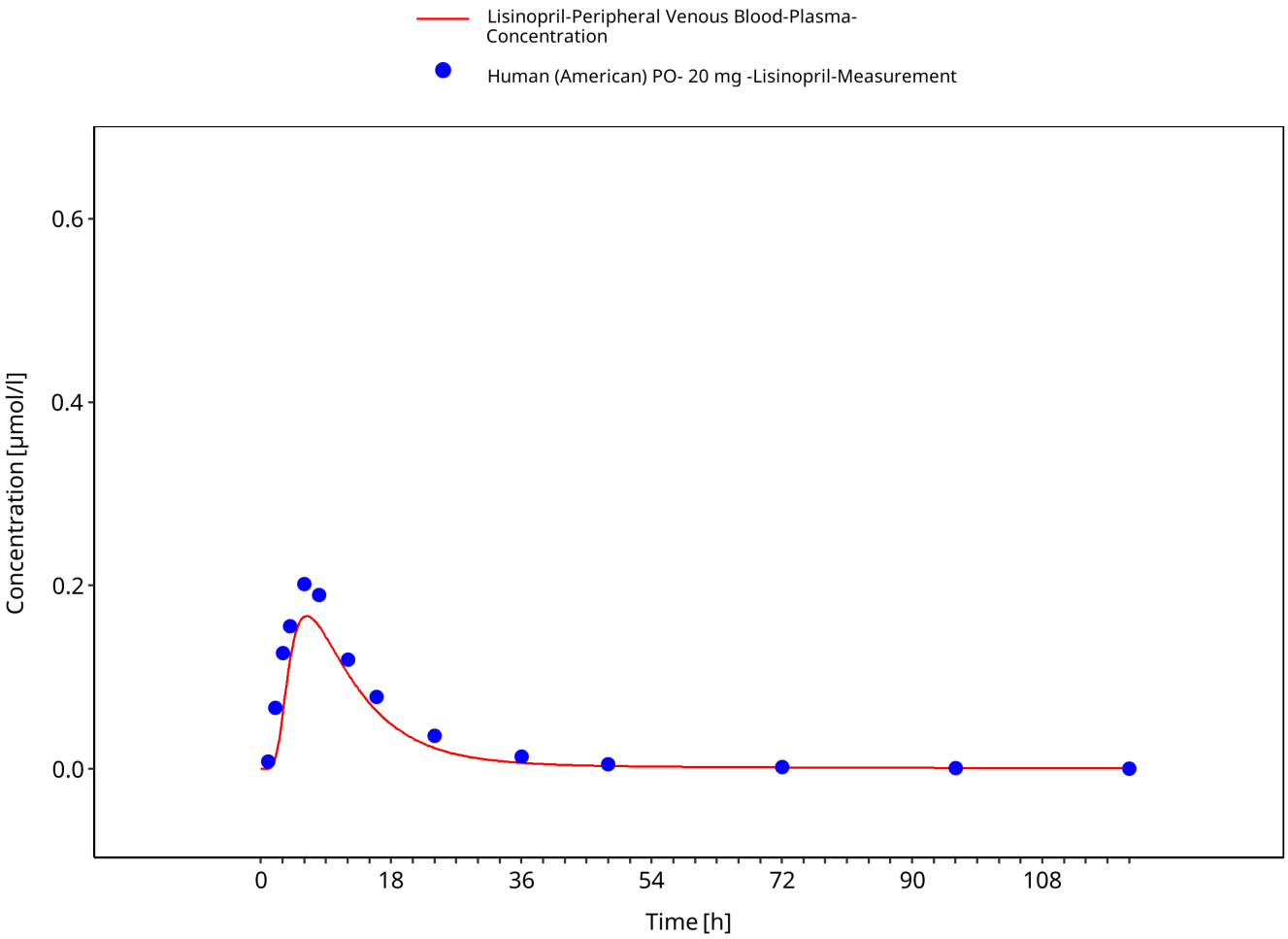

Figure 3-8: Lisinopril - PO, Mojaverian fasted 20mg

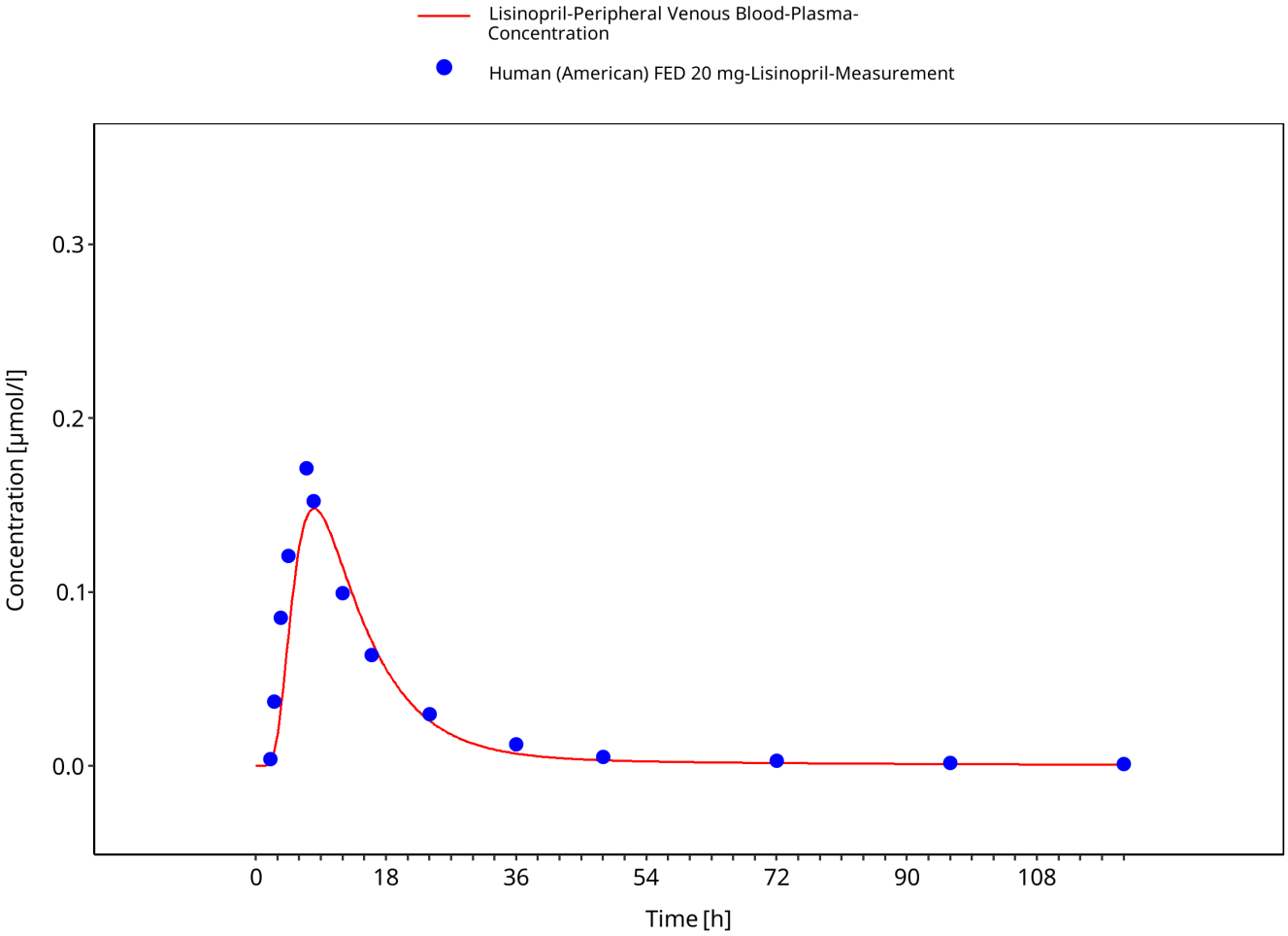

Figure 3-9: Lisinopril - PO, Mojaverian fed 20mg

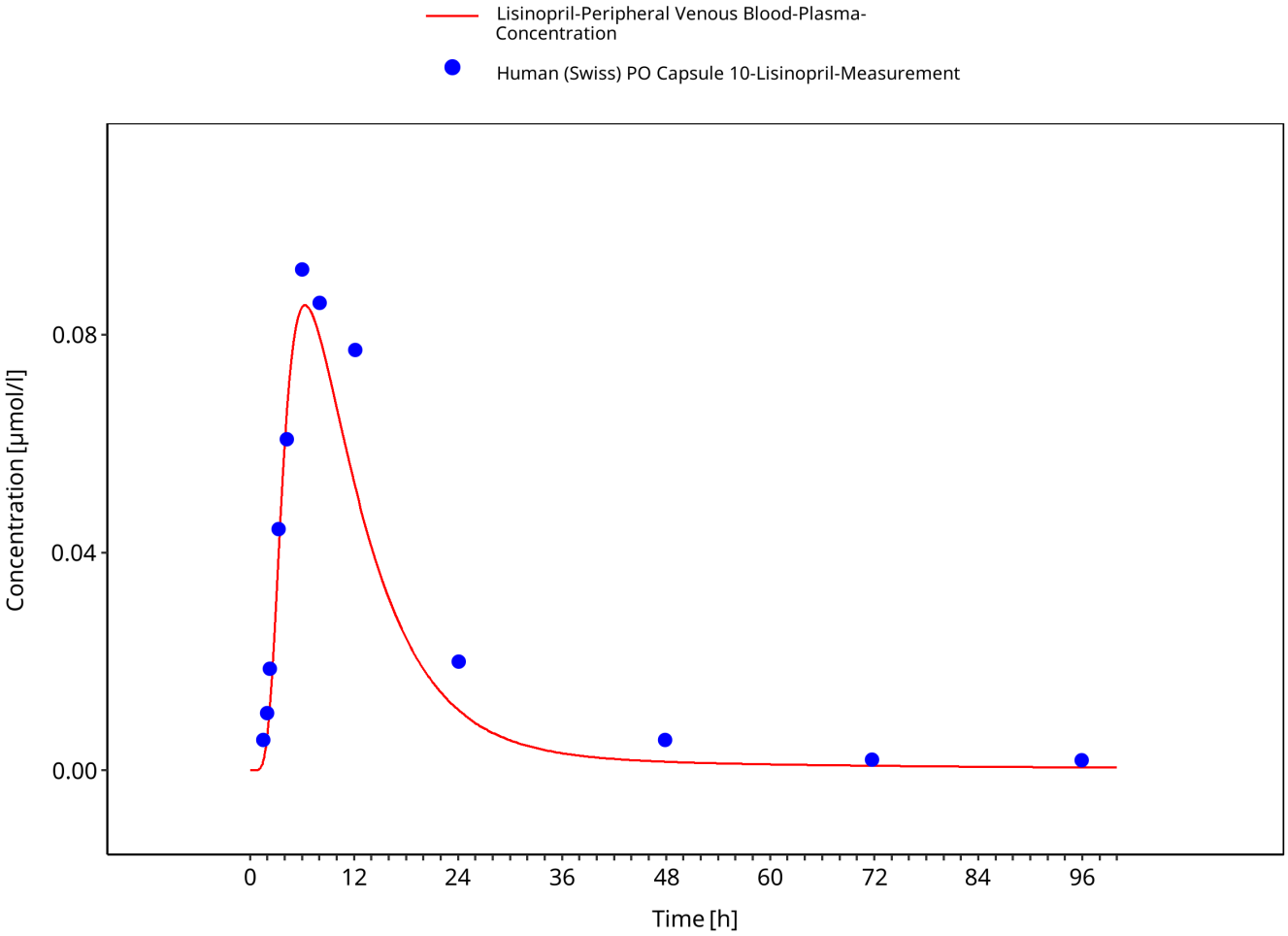

Figure 3-10: Lisinopril - PO, Ulm fed 10mg

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of Lisinopril in adults.

5 References

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